UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 30, 2002

MEMORANDUM

SUBJECT: Revised HED Risk Assessment for Lindane. DP Barcode D280622
Reregistration Case # 0315; PC code 009001

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Attached is HED's revised risk assessment of the insecticide, lindane for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This document updates the January 9,2002 version of the risk assessment to reflect current HED policy on risk aggregation. The disciplinary science chapters and other supporting documents have also been revised in response to public comment where necessary and are available as attachments to this document. This chapter incorporates information from the toxicology assessment by Suhair Shallal, the residue chemistry assessment and dietary exposure and risk estimates by Thurston Morton, and the occupational and residential exposure assessment by Dave Jaquith. The disciplinary science chapters and other supporting documents for the lindane RED are also included as attachments as follows:

Revised Report of the Hazard Identification Assessment Review Committee. Suhair Shallal (6/18/01, 014595)
Report of the FQPA Safety Factor Committee. Brenda Tarplee (8/2/00; 014272)
Revised Product and Residue Chemistry Chapter. Thurston Morton (12/11/01, D279259)
Toxicology Chapter. Suhair Shallal (9/28/00, D269338)
Occupational and Residential Exposure Assessment and Revision. David Jaquith (3/2001, D254759; 6/5/2001, D275419)
Revised Dietary Exposure and Risk Estimates for Reregistration. Thurston Morton (12/13/01, D279260)
Dietary Risk and Exposure Estimate for Lindane through Subsistence Diets for Indigenous People of Alaska. Thurston Morton (1/8/02, D280076)
Environmental Fate and Effects Chapter. Nicholas Federoff (6/22/00, D254762, D254764, D239249, D240496, D257803, D255772)

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I. EXECUTIVE SUMMARY

A. Use and Major Formulations

Lindane (gamma isomer of hexachlorocyclohexane, γ-HCH) is a broad-spectrum organochlorine insecticide/acaricide which has been used on a wide range of soil-dwelling and plant-eating (phytophagous) insects. Worldwide, it is commonly used on a wide variety of crops, in warehouses, in public health to control insect-borne diseases, and (with fungicides) as a seed treatment. Lindane is also presently used in lotions, creams, and shampoos for the control of lice and mites (scabies) in humans; these pharmaceutical uses are regulated by FDA. In the U.S., the only registered food/feed use is seed treatment for field and vegetable crops.

Lindane may be found in formulations with a host of fungicides and insecticides. Labels for products containing it must bear the Signal Word WARNING. Some formulations of lindane are classified as Restricted Use Pesticides (RUP), and as such may only be purchased and used by certified pesticide applicators. Lindane is no longer manufactured in the U.S. According to a REFS search, conducted on 5/29/01, there are approximately 34 federally registered end-use products (EPs) containing lindane as the active ingredient and three Section 24°C registrations. Lindane end-use products are formulated as dust (D), wettable powder (WP), emulsifiable concentrate (EC), flowable concentrate (FlC), and ready-to-use (RTU) solution.

The reregistration of lindane is being supported by Centre International d'Etudes du Lindane (CIEL) and its member company holding U.S. registrations, Inquinosa, S.A. Currently, Inquinosa does not have any registered lindane end-use products. In 1993, CIEL offered to voluntarily cancel all crop uses of lindane except seed treatment and certain non-food uses. The Agency considers lindane seed treatment as a food use requiring tolerances based on existing data from radiolabeled studies indicating uptake of residues from the treated seeds into the aerial portion of the growing crop.

B. Regulatory History

Lindane is a List A reregistration pesticide. A Reregistration Standard for Lindane was issued 9/85. The Residue Chemistry Chapter to the Reregistration Standard was issued on 6/7/85, an addendum on 9/5/85, and an Update on 1/31/91. The Reregistration Standard along with its Science Chapters summarized the available data for each residue chemistry guideline and specified what additional data are required for reregistration purposes. Data Call-In (DCI) Notices for lindane were issued by the Agency on 9/30/91, 3/3/95, 10/13/95, and 3/31/97. The information contained in this document outlines the current Residue Chemistry Science Assessments with respect to supporting seed treatment uses of lindane, as well as the reregistration of the pesticide.

In 1983, EPA concluded a major Special Review effort of lindane based on carcinogenicity, fetotoxicity/teratogenicity, reproductive effects, and acute effects on aquatic organisms. This effort resulted in the cancellation of indoor uses of smoke fumigation devices

and greatly limited the use of pet dips on dogs. In addition, there were uses that were allowed to continue only if certain imposed restrictions were implemented. The restrictions were based on the degree of associated hazards, and included changes in warning labels, the wearing of protective clothing, and restrictions to limit uses to certified pest control operators.

In 1995, EPA announced (FR Vol. 60, No. 143, 38329-38331, 7/26/95) its decision not to initiate a Special Review of lindane based on worker health concerns arising from studies showing irreversible renal effects in the rat. The Agency has determined that these effects occur only in the kidneys of male rat and are not relevant for human risk assessment.

Tolerances are currently established under 40 CFR §180.133 for residues of lindane *per se* in/on various raw agricultural commodities at 0.01 ppm (pecans) to 3 ppm (cucumbers, lettuce, melons, mushrooms, pumpkins, squash, summer squash, and tomatoes). Lindane tolerances are also established at 4 ppm in the fat of meat from hogs and at 7 ppm in the fat of meat from cattle, goats, horses, and sheep. No tolerances have been established for processed food/feed commodities. Adequate methods are available for the enforcement of tolerances for residues of lindane *per se* in/on plant and animal commodities.

The only food/feed use of lindane which is being supported for reregistration is seed treatment on canola, spinach, and cereal grains (excluding rice and wild rice). Seed treatment uses on broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, radishes, and spinach are no longer being supported for reregistration by Inquinosa. In addition, the established tolerances for the following commodities will be revoked because no registrants have committed to support the foreign or domestic uses for: apples, apricots, asparagus, avocados, celery, cherry, collards, cucumbers, eggplants, grapes, guavas, kale, kohlrabi, mangoes, melons, mushrooms, mustard greens, nectarines, okra, onions (dry bulb only), peaches, pears, pecans, peppers, pineapple, plums (fresh prunes), pumpkins, quinces, squash, strawberries, summer squash, swiss chard and tomatoes.

C. Hazard Identification and Dose-Response Assessment

The toxicology database for lindane is complete with respect to the OPPTS Guideline requirements. In acute toxicity studies, lindane is a moderately toxic compound, EPA toxicity class II. It is neither an eye irritant nor dermal sensitizer.

The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation no observable adverse affect levels (NOAELs). In light of the developing Agency policy on use of toxicology studies employing human subjects, HED selected doses and endpoints for risk assessment based solely on animal studies.

The primary effect of lindane is on the nervous system; in acute, subchronic, and developmental neurotoxicity studies and chronic toxicity/oncogenicity studies, lindane appears to cause neurotoxic effects including tremors, convulsions and hypersensitivity to touch. This is

further corroborated by the published literature in which human exposure has been seen to produce neurologic effects. Lindane also causes renal and hepatic toxicity via the oral, dermal and inhalation routes of exposure as seen in subchronic, 2-generation reproduction and chronic toxicity studies in the rat, as well as in studies in the open literature (S. Shallal, D274510).

In developmental toxicity studies, developmental effects were only seen at levels where maternal toxicity was also evident. In the rat developmental study, the developmental effects (extra rib and total skeletal variations) were seen at dose levels (20 mg/kg/day) greater than maternal toxicity (10 mg/kg/day). In the reproductive toxicity study, both systemic and developmental LOAELs are 13 mg/kg; however a qualitative difference in maternal and offspring effects (reduced body weight of maternal animals and reduced viability and delayed maturation in pups) indicates an increased susceptibility to exposure. This is further corroborated by a developmental neurotoxicity study in which a qualitative and quantitative increase in susceptibility is seen. At the high dose (13.7 mg/kg/day) , animals in the F_0 generation have a reduced body weight and body weight gain while at the mid-dose (5.6 mg/kg/day), F_1 animals have a reduced survival rate, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation as compared to controls.

The OPP/Cancer Assessment Review Committee (CARC) has completed the review of newly submitted carcinogenicity study in CD-1 mice along with other data. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC has classified lindane into the category **"Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"** based on an increased incidence of benign lung tumors in female mice only. The Committee, therefore, recommended that the quantification of human cancer risk is not required. (S. Diwan, 11/29/01, TXR NO. 0050297)

The International Programme on Chemical Safety (IPCS, 1991) states that lindane does not appear to have mutagenic potential. The available mutagenicity studies are negative; they include a dominant lethal mutation assay, sister chromatid exchange assay and mammalian cell culture gene mutation in V79 cells. However, these studies have been classified as unacceptable by EPA.

The Food Quality Protection Act (FQPA) Safety Factor Committee evaluated the hazard and exposure data to determine if the 10x safety factor should be retained. The Committee recommended that the **FQPA safety factor** be **reduced** to 3X due to the following considerations: 1) the toxicology data base is complete; 2) the available data provide no indication of quantitative or qualitative increased susceptibility in rats from *in utero* exposure to lindane in the prenatal developmental study; 3) the offspring effects seen in the developmental neurotoxicity study were the same as those seen in the two-generation reproduction study (no additional functional or morphological hazards to the nervous system were noted); 4) adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment; 5) although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a

new study is not required because: a) The developmental toxicity study in rabbits and rats using a subcutaneous route of administration shows no developmental effects at the maternally toxic dose, b) The skeletal effects observed in the developmental toxicity study in rats, with gavage as the route of administration, are within historical controls, c) More severe maternal effects are seen in the rabbit study with subcutaneous administration, d) The rat appears to be the more sensitive species for developmental effects, e) A developmental neurotoxicity study has already been submitted. and 6) there are currently no residential uses.

D. Exposure Assessment

The HED Metabolism Assessment Review Committee (T. Morton, 8/30/00, D267069) concluded that the total radioactive residues (TRRs) should be used for risk assessment purposes and calculation of dietary burdens, pending receipt of additional metabolism data. The ChemSAC recommended comparing the results from the dietary analysis using the TRRs with the results from a dietary analysis based on feeding studies. Exposure to lindane was determined by using the ratio (ppm TRR/ppm lindane parent). The results from the dietary analysis using the feeding study results and adjusting the lindane residues by the above ratio are summarized in this assessment. The Biological and Economic Analysis Division (OPP/BEAD) verified the registrant's percent market share estimate for lindane (I. Yusuf email, 7/17/00). A canola processing study for lindane was recently reviewed (T. Morton, D269388, 5/10/01). Lindane was not detected in bleached/deodorized canola oil (<0.005 ppm). Therefore, ½ LOQ (0.0025 ppm) will be used as the DEEM™ adjustment factor 1. DEEM™ default concentration factors (adjustment factor 1) were used for all other commodities.

The Indigenous Peoples of the Arctic region of the U.S. (Alaska) rely heavily on subsistence diets as their food source. Therefore, it is considered appropriate for the Agency to perform a supplementary dietary risk and exposure assessment to assess the risk to the Indigenous People from worldwide use and manufacture of lindane. The dietary risk to Indigenous People of Alaska for Lindane has been revised. (T. Morton, D280076, 1/8/02). Using the limited data available, we have extrapolated from this information and knowledge of the standard diet of the indigenous people of Alaska to arrive at a conservative estimate. The data used in this assessment is based on actual residues found in animal tissues in conjunction with typical subsistence diet consumption rates. Because factors such as bioaccumulation of lindane and the cumulative effects of combinations of chemicals which act through a common mode of action have not been incorporated into this assessment, it is therefore difficult to know the full range of residue to which indigenous populations may be exposed.

Lindane does not occur naturally in the environment. Once released it can partition into all environmental media. Lindane has been detected in air, surface water, groundwater, sediment, soil, ice, snowpack, fish and other aquatic organisms, wildlife, and humans. Lindane has been found in pristine environments; the pathway for contamination is varied and complex depending on atmospheric and oceanic circulation, gas/particle partitioning, and solubility of the substance and the food chain. Monitoring data has shown that Lindane is detectable across the entire North American continent, from Washington D.C., Denver, Colorado, and the Niagra

River water samples to air samples over the Adirondack Mountains in New York, Newport News, Virginia and Ontario, Canada, as well as, soil samples from around the Great Lakes and the Gulf of Mexico.

The Environmental Fate and Effects Division (EFED) evaluated the potential for lindane to contaminate water. The presence of lindane in the environment, due to previous widespread agricultural use, is well documented in U.S. data bases. For example, In the U.S. EPA STORET data base, 720 detections (after culling of data to eliminate dubious data) in ground water were reported between the years 1968 and 1995, in nearly all regions of the country, with especially high numbers of detections in the South and West. For these 720 detections, the median and mean concentrations were 0.01 and 11 μg/L, respectively. For surface waters, 8775 detections were reported with median and mean concentrations of 0.005 and 0.18 μg/L. STORET Detections were reported in nearly all regions of the conterminous U.S. In the USGS NAWQA study, lindane was detected in 2.58% of surface water samples (0.67% at levels greater than 0.05 μg/L, maximum concentration reported was 0.13 μg/L). For groundwater, USGS NAWQA reported a detection frequency of 0.1 % (0.07% at levels greater than 0.01 μg/L, maximum concentration reported was 0.032 μg/L).

EFED models (GENEEC and SCI-GROW) were used to determine aquatic EECs resulting from seed treatment uses. Wheat has the highest application rate in terms of lbs a.i per acre and was used as the model crop scenario. The SCI-GROW model was used to estimate concentrations of lindane in groundwater. The Tier I screening model GENEEC was used to estimate surface water concentrations.

Occupational exposure scenarios can be described as short term (1-7 days), intermediate term (7 days to several months), and long term or chronic (several months to a lifetime). Most of the lindane exposure scenarios are appropriately described as short and intermediate term.

HED has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during usual use-patterns associated with lindane. Based on the use patterns and potential exposures described above, 5 major exposure scenarios were identified to represent the extent of lindane uses: (1) mixing/loading/application of formulations for on-farm seed treatment, (2) mixing/loading and applying liquid with commercial seed-treatment equipment, (3) bagging and otherwise handling treated seeds, (4) mixing/loading of treated seed for planting, (5) planting treated seeds.

Mixer/loader/applicator exposure data for lindane were required since one or more toxicological criteria had been triggered. Requirements for applicator exposure studies are addressed by Series 875 Group A (formerly Subdivision U of the Pesticide Assessment Guidelines). Two lindane specific exposure studies, one addressing commercial seed treatment and the other on-farm treatment, have been utilized to estimate exposure. In the case of mixing/loading and planting of treated seed, data from PHED V1.1 were used for exposure estimation. It was assumed that exposures from treated seed would resemble those from mixing/loading or application of granular formulations.

E. Risk Assessment/Characterization

Dietary (food source)- Anticipated residues (DP Barcode D279260, T. Morton, 12/4/01) were provided for all commodities and used when calculating the dietary risk associated with lindane for the RED. Although the database for lindane is substantially complete, additional data are needed to eliminate the uncertainties associated with the exposure/risk assessment. The anticipated residue values are the best estimates HED can provide using the residue data available at the time of the RED. These values have an inherent uncertainty associated with variations in analytical methods, geographical representation of field trials, seasonal variation of residue levels, use of TRR from metabolism studies, etc.

The acute dietary exposure analysis was a tier 3 probabilistic assessment. In both acute and chronic risk assessments, exposure was compared to a population adjusted dose, (PAD), which is the reference dose (RfD) reflecting application of the FQPA 3X safety factor. HED considers dietary residue contributions greater than 100% of the PAD to be of concern. The dietary assessment was conducted using percent crop treated (%CT) and total radioactive residues (TRRs) from plant metabolism studies and from poultry and ruminant metabolism studies. A second dietary assessment was conducted which incorporated data generated from poultry and ruminant feeding studies which provided lindane only residue values. In this assessment, an average lindane only residue value was calculated from three dose levels and multiplied by the ratio of TRR:lindane derived from the corresponding poultry or ruminant metabolism studies. (Average lindane residue from feeding study X TRR from metabolism study/lindane residue from metabolism study). The following assessments yielded higher percent aPAD and cPAD values which were used to calculate drinking water levels of comparison (DWLOCs).

Acute Dietary (Food). The acute dietary analysis for lindane was conducted using the Dietary Exposure Evaluation Model (DEEM™) software. Results are reported as a percentage of the acute Population Adjusted Dose (aPAD) for the 99.9th percentile of the population. Estimated acute dietary exposure is below HED's level of concern for all population subgroups at the 99.9th percentile. The maximum dietary risk estimate is 17 % of the acute PAD (% aPAD) for the population subgroup All Infants and 7 % of the aPAD for the U.S. Population when the feeding studies were adjusted using the metabolism studies.

Chronic Dietary (Food). The chronic dietary analysis for lindane was conducted using the DEEM™ software. Results are reported as a percentage of the chronic Population Adjusted Dose (cPAD). Estimated chronic dietary risk is below HED's level of concern. The resulting risk estimates are 3 % of the chronic PAD (% cPAD) for the U.S. Population and 11 % of the cPAD for Children 1-6 years of age (the most highly exposed population subgroup. The remaining population subgroups were <6 % of the cPAD when the feeding studies were adjusted using the metabolism studies.

Acute Drinking Water. Acute DWLOCs were calculated based on the acute dietary exposure and default body weights and water consumption figures. The EECs for surface water (GENEEC) and the EECs for groundwater (SCI-GROW) were less than the acute DWLOCs for

all sub-populations indicating that acute aggregate exposure to lindane in food and water is less than HED's level of concern.

Chronic Drinking Water. Chronic DWLOCs were calculated based on the chronic dietary (food) exposure and default body weights and water consumption figures. The EECs for surface water (GENEEC) and the EECs for groundwater (SCI-GROW) were less than the chronic DWLOC's, indicating that chronic exposure to lindane in food and water is less than HED's level of concern.

Special Populations. The Indigenous Peoples of the Arctic region of the U.S. (Alaska) rely heavily on subsistence diets as their food source. Therefore, HED performed a revised supplementary chronic dietary risk and exposure assessment to assess the risk to Indigenous People from worldwide use and manufacture of lindane (T. Morton, D280076, 1/8/02). Because the annual harvest rates were divided by 365 to obtain daily harvest rates, and the daily intake rates were used in the assessment, no acute dietary exposure analysis was conducted. The chronic dietary exposure analysis used subsistence food harvest amounts and total HCH residues in traditional foods, and adjusted the HCH exposure to obtain lindane exposure. To estimate subsistence food intake rates, EPA used data from the Alaska Department of Fish and Game Division of Subsistence data base. This data base provides subsistence food harvest amounts for nearly 180 Alaskan communities from 1990-2001. Since marine mammals represents the largest portion of the subsistence harvest, HED used the community with the highest representative seal harvest, the community with the highest walrus harvest, and the community with the highest whale harvest to estimate subsistence intake rates. Other subsistence food sources (e.g., land mammals, other marine mammals, fish, and birds) from the corresponding Alaskan community were also included in estimating subsistence intake.

The combined subsistence food source exposures from Community 1 (the community with highest total intake of the three communities) amounts to 0.282065 mg/day HCH. Adjusting total HCH to obtain lindane only exposure yields a lindane exposure for Community 1 of 0.04231 mg/day. (Total HCH is adjusted by factors of 0.15 and 0.03 since lindane represents between 3 and 15% of total HCH residues). Based on revised exposure estimates and assuming a male adult body weight of 70 kg, the chronic dietary risk to adult male Indigenous People ranges from 0.000055 - 0.0006 mg/kg body weight/day which is between 3 and 38 % of the cPAD. This is below HED's level of concern (cPAD = 0.0016 mg/kg bw/day). The revised estimate of chronic dietary risk to adult female Indigenous People (body weight of 60 kg) ranges from 0.000064 - 0.0007 mg/kg bw/day or from 4 to 44 % of the cPAD, also below HED's level of concern. Assuming a child body weight of 10 kg and adjusting adult intake by a factor of 0.53 to account for adult vs child subsistence meat intake, the revised lindane dietary risk estimates for children from subsistence food consumption range from 0.0002 - 0.0022 mg/kg bw/day or from 13 to 138% of the cPAD.

Residential Risk Estimates. No residential exposure scenarios have been identified for pesticide uses of lindane and therefore no risk estimates will be presented in this document for non-occupational exposure to lindane.

Occupational Risk Estimates. The Agency has refined occupational and residential risk estimates using new information, including the Pesticide Handlers Exposure Database (PHED, version 1.1), additional information on cultural practices in on-farm and commercial seed treatment, and the toxicological endpoints chosen by OPP's Hazard Identification Assessment Committee. The FQPA uncertainty factor of 3X is not applicable to occupational risk assessments. Resulting risk estimates are reported as Margins of Exposure (MOEs), and compared to the target MOE, which is 100 for all lindane occupational exposure scenarios.

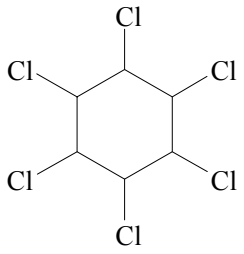
The Agency has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during usual use-patterns associated with lindane. The exposure scenario descriptions based on the use pattern of lindane are presented in Table 12. The daily exposures, as well as the resulting short and intermediate term MOEs are presented in Table 13. A total of 11 dermal and inhalation MOEs were calculated for the various scenarios. The analysis indicates that the MOEs are of concern (MOE<100) for commercial seed treaters who mix, load and apply a liquid formulation of lindane to canola seed at 1.5 lb/100 lb seed. Dermal MOEs range between 5.3 and 40 depending on the capacity of the seed treatment facility, and the corresponding inhalation MOEs range from 2.6 to 20. MOEs are of concern for seed handlers (those not directly handling the liquid formulation) at high capacity seed treatment facilities since the inhalation MOE is 20. On farm handling of a dry formulation of lindane to treat seed results in a dermal MOE of 19 which is of concern. All other scenarios result in MOEs that are not of concern.

Aggregate Exposure and Risk. The Agency considered aggregate exposure and risk estimates for residents who might be exposed to lindane from multiple sources, such as residential use, food, and water. Since no residential exposure is expected, an aggregate risk estimate was not calculated.

II. Physical and Chemical Properties

The chemical structure and physical properties of Lindane are given below.

Empirical Formula:	$C_6H_6Cl_6$
Molecular Weight:	290.9
CAS Registry No.:	58-89-9
PC Code:	009001



Lindane is a white crystalline solid with a melting point of 112-113 °C, specific gravity of 1.85, octanol/water partition coefficient (K_{ow}) of 3135, and vapor pressure of 9.4 x 10^{-6} mm Hg at 20 C. Lindane is slightly soluble in water (10 ppm at 20 C) and in most organic solvents,

including acetone and aromatic and chlorinated hydrocarbons. Lindane is only slightly soluble in mineral oils. Lindane is stable to light, heat, air, and strong acids, but decomposes in alkali solutions to trichlorobenzenes and HCl.

Fate studies show that lindane is both moderately mobile (mean K_{oc} = 1368) and highly persistent (soil half life of 2.6 years). It is resistant to photolysis and hydrolysis (except at high pH), and degrades very slowly by microbial actions. Degradates are predominantly pentachlorocyclohexane, 1,2,4,-trichlorobenzene, and 1,2,3-trichlorobenzene. Also, lindane can possibly transform to the alpha and beta isomers of hexachlorocyclohexane by biological and phototransformation, although this issue remains to be conclusively resolved. Metabolites are not quantified since they comprise less than 10% of the total residue; they are also found in rat metabolism studies and have therefore been indirectly evaluated for their toxicologic effects.

III. Hazard assessment

A. Toxicology Assessment

Based on available information to date, the Agency has determined that the adverse effects of primary concern for lindane are those related to neurotoxicity.

Organochlorine pesticides, such as lindane, are known to cause delayed neurotoxic effects. Symptoms include a number of clinical signs and symptoms, including headaches, dizziness, nausea, vomiting, diarrhea and increased urination, blurred vision, labored breathing, muscle paralysis, slow heart rate, respiratory depression, convulsions, coma and even death. Numerous toxicological studies using laboratory animals are available addressing most of these toxicological endpoints for lindane. In acute, subchronic and developmental neurotoxicity studies, it was found to cause neurotoxic effects including tremors, convulsions, decreased motor activity, increased forelimb grip strength, hypersensitivity to touch, hunched posture and decreased motor activity habituation. There also appears to be a greater susceptibility to exposure by offspring compared to parental animals in the developmental neurotoxicity study. Lindane has also been implicated as a possible endocrine disruptor in birds, mammals and possibly fish. Further studies to ascertain the validity of such evidence is necessary to make informed risk assessment decisions.

Lindane is distributed to all organs at measurable concentrations within a few hours after oral administration. The highest concentrations are found in adipose tissue. The metabolism of lindane is initiated through one of several pathways: Dehydrogenation leading to γ–HCB, dehydrochlorination leading to formation of γ–pentachlorocyclohexene, dechlorination leading to formation of γ–tetrachlorohexene, or hydroxylation leading to formation of hexachlorocyclohexanol. Further metabolism leads to a large number of metabolites. Lindane is converted by enzymatic reactions, mainly in the liver.

Lindane appears to affect the liver and kidney in male rats when administered through the oral, dermal or inhalation routes of exposure. Kidney lesions in males indicative of alpha 2μ

globulin accumulation were observed in animals treated with ≥10 ppm, but are not considered relevant to human health risk assessment The liver effects include: incidence of periacinar hepatocytic hypertrophy which was significantly ($p \leq 0.01$) increased in male and female rats dosed at 100 ppm (4.81 and 6.00 mg/kg/day, respectively). In addition, increased liver and spleen weights, and decreased platelets were also noted.

Lindane is not considered teratogenic when administered orally or subcutaneously. Developmental toxicity NOAELs were found to be at levels equal to or greater than maternal NOAELs, except in the developmental neurotoxicity study. The developmental neurotoxicity LOAEL was 5.6 mg/kg/day (NOAEL is 1.2 mg/kg/day) based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation compared to a maternal toxicity LOAEL of 13.7 mg/kg/day (NOAEL is 5.6 mg/kg/day) based on decreased body weight gains, decreased food consumption, and increased reactivity to handling.

The data base for reproductive toxicity is considered complete. Both parental and offspring LOAELs are 13 mg/kg; however there is a qualitative difference in the severity of effects. In the parental animals, toxicity was seen in the form of reduction in body weight gain during gestation while offspring toxicity was correlated with decreases in pup viability and pup body weight in the F_1 and F_2 generations as well as delayed maturation in the F_2 generation. Evidence for quantitative increase in susceptibility could not be ascertained due to the wide spread in the doses tested.

The OPP/Cancer Assessment Review Committee (CARC) has completed the review of newly submitted carcinogenicity study in CD-1 mice along with other data. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC has classified lindane into the category **"Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"** based on an increased incidence of benign lung tumors in female mice only. The Committee, therefore, recommended that the quantification of human cancer risk is not required.

In a mammalian cell gene mutation assay and an in vivo sister chromatid exchange assay, no mutagenic response was detected. These studies were classified as unacceptable by EPA. The open literature suggests, however, that technical grade HCH (hexachlorohexane; 6.5% γ–HCH) may induce some mutagenic activity as evidenced in a dominant lethal mutation assay and sister chromatid exchanges. It has been noted, however, by the IPCS that lindane does not appear to have a mutagenic potential.

The acute toxicity studies for lindane are summarized in Table 1, and the toxicology profile for lindane is summarized in Table 2. The toxicology database required to support the Reregistration of lindane is essentially complete. All required toxicology studies have been submitted and reviewed by Agency scientists.

Table 1. Guideline Acute Toxicity Studies for Lindane

STUDY TYPE	MRID	CATEGORY	RESULT
81-1Acute oral-rat	00049330	II	LD_{50} 88 mg/kg - males 91 mg/kg - females
81-2 Acute dermal-rabbit	00109141	II	LD_{50} 1000 mg/kg - males 900 mg/kg - females
81-3 Acute inhalation-rat	Acc. 263946	III	LC_{50} 1.56 mg/L both sexes
81-4 Eye irritation-rabbit	Acc. 263946	III	PIS = 0.6 no corneal involvement irritation cleared after 24 hours
81-5 Dermal irritation-rabbit	Acc. 262946	IV	PIS = 0 not an irritant
81-6 Dermal sensitization- g. pig	Acc. 262946	NA	not a sensitizer

Table 2. Guideline Toxicology Studies for Lindane

Guideline No./ Study Type	MRID No. -year/ Classification	Results
870.3250 90-Day dermal toxicity in rat	41427601 -1990 acceptable/ guideline	NOAEL = 10 mg/kg/day LOAEL = 60 mg/kg/day based on lesion in the liver in males and females and adrenal gland weight increases in males
870.3465 90-Day inhalation toxicity in rat	00255003 -1983 acceptable/guideline	NOAEL = 0.025 mg/kg/day LOAEL = 0.13 mg/kg/day based on transient microscopic lesions in the kidney and increased kidney weights in the males.
	40873501 -1988 acceptable/guideline	NOAEL = 0.08 mg/kg/day LOAEL = 0.25 mg/kg/day based on death of one male and one female
870.3700a Prenatal developmental in rat	00062656 -1976 (Subcutaneous) unacceptable/ nonguideline	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on reduced body weight **Developmental** NOAEL = >30 mg/kg/day LOAEL = not identified
	42808001 -1971 acceptable/ guideline	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 10 mg/kg/day based on reduced body weight and food consumption **Developmental** NOAEL = 10 mg/kg/day LOAEL = 20 mg/kg/day based on skeletal variation.
870.3700b Prenatal developmental in rabbit	00062658 -1976 (Subcutaneous) unacceptable/ nonguideline	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on clinical signs, mortality, reduced body weight **Developmental** NOAEL ≥15 mg/kg/day LOAEL = not identified
	42808002 -1971 unacceptable/ nonguideline	**Maternal** NOAEL ≥20 mg/kg/day LOAEL = not identified **Developmental** NOAEL ≥20 mg/kg/day LOAEL = not identified

Guideline No./ Study Type	MRID No. -year/ Classification	Results
870.3800 Reproduction and fertility effects in rat	42246101 -1991 acceptable/ guideline	NOAEL = 1.7 mg/kg/day ♀; 0.09mg/kg/day ♂ LOAEL = 13 mg/kg/day ♀ based on reduced body weight; 1.7 mg/kg/day ♂ based on increased kidney weight and alpha-2 globulin accumulation (not relevant for humans) NOAEL for reproductive toxicity =1.7 mg/kg/day (20 ppm) LOAEL for reproductive toxicity = 13 mg/kg/day (150 ppm) based on reduced pup body weights and decreased viability in both generations and delayed maturation of the F_2 pups
870.4300 Carcinogenicity mice	special study -1987	see below- literature studies
870.4100a Chronic toxicity rodents 870.4200 Carcinogenicity rats	41094101 41853701 42891201 -1993 acceptable/ guideline	NOAEL =0.6 mg/kg/day LOAEL = 4.8 mg/kg/day ♂; 6 mg/kg/day ♀ based on periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets **no evidence of carcinogenicity**
870.5300 Gene Mutation Mammalian Cell	00144500 -1985 unacceptable/ guideline	negative
870.5915 In Vivo Sister Chromatid Exchange	00024504 -1984 unacceptable/ guideline	negative
870.5450 dominant lethal assay	00062657 unacceptable/ guideline	negative
870.6200a Acute neurotoxicity screening battery in rat	44769201 -1999 acceptable/ guideline	NOAEL = 6 mg/kg/day ♀; 20 mg/kg/day ♂ LOAEL = 20 mg/kg/day (♀) based on increased grip strength and motor activity. 60 mg/kg/day (♂) based on tremors, convulsions, decreased motor activity and increased grip strength.
870.6200b Subchronic neurotoxicity screening battery in rat	44781101 -1999 acceptable/ guideline	NOAEL = 7.9 mg/kg/day♀; 7.1 mg/kg/day♂ LOAEL = 30.2 mg/kg/day and 28.1 mg/kg/day based on hypersensitivity to touch and hunched posture

Guideline No./ Study Type	MRID No. -year/ Classification	Results
870.6300 Developmental neurotoxicity in rat	45073501 -1999 acceptable/ guideline	**Maternal** NOAEL = 5.6 mg/kg/day LOAEL = 13.7 mg/kg/day based on decreased body weight gains, decreased food consumption, and increased reactivity to handling. **Offspring** NOAEL = 1.2 mg/kg/day LOAEL = 5.6 mg/kg/day based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.
870.7600 Dermal penetration	40056107-1987 rat 40056108-1987 rabbit acceptable/ guideline	18 % absorption at 10 hours
literature studies		
Feldmann, RJ and HI Maibach, Percutaneous penetration of some pesticides and herbicides in man, Toxicology and Applied Pharmacology, 28:126-132 (1974).	Non-guideline	~10% absorption in humans
Other: Tumorigenic responses to lindane in mice: potentiation by a dominant mutation.	Special study dietary administration-1987	NOAEL = not identified LOAEL = 23 mg/kg/day (160 ppm) based on induction of tumors, increased liver weights, increased enzyme activity, and irreversible Clara cell hyperplasia in lung **evidence of carcinogenicity**- induction of liver and lung tumors in the agouti, pseudoagouti and black mouse strains—only females; only 0 and 160 ppm

Other Literature Studies

In addition to the developmental and reproduction studies submitted to the Agency to fulfill the OPPTS Guidelines, HED's Hazard Identification Assessment Review Committee (HIARC) evaluated a segment of the extensive body of information published in the open literature dealing with lindane. These studies show that exposure to lindane, both transplacental and via mother's milk, is possible and that such exposure may result in adverse developmental effects on human offspring. According to Karmaus et al (1995), females exposed to lindane risk having offspring with reduced birthweight and length. Pompa et al (1994) has also been able to show that transfer of lindane and pentachlorobenzene from mother to newborn rabbits can occur. Rivera et al (1990) found that early postnatal exposure to lindane may induce behavioral changes in developing rats. Evidence of reproductive failure and fetotoxicity in mice has been compiled by Sircar et al.

B. Dose Response Assessment

i. Determination of Susceptibility

There was evidence of qualitative increased susceptibility in the rat multi-generation reproduction study: Both parental and offspring LOAELS are 13 mg/kg; however there is a qualitative difference in the severity of effects. In the parental animals, toxicity was seen in the form of reduction in body weight gain during gestation while offspring toxicity was correlated with decreases in pup viability and pup body weight in the F_1 and F_2 generations as well as delayed maturation in the F_2 generation. Evidence for quantitative increase in susceptibility could not be ascertained due to the wide spread in the doses tested.

There is also quantitative increased susceptibility demonstrated in the rat developmental neurotoxicity study: Maternal toxicity observed at 120 ppm (13.7 mg/kg/day, LOAEL) is based on decreased body weight gains, decreased food consumption, and increased reactivity to handling (maternal NOAEL is 50 ppm; 5.6 mg/kg/day). Offspring toxicity was observed at 50 ppm (5.6 mg/kg/day, LOAEL) and is based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation (NOAEL is 10 ppm; 1.2 mg/kg/day).

The offspring effects seen in the developmental neurotoxicity study were the same as those seen in the two-generation reproduction study - no additional functional or morphological changes in the nervous system were noted. In the open literature, lindane is found in mother's milk and metabolites of lindane have been shown to cross the placental barrier.

The Food Quality Protection Act (FQPA) Safety Factor Committee met on August 2, 2000 and evaluated the hazard and exposure data to determine if the 10x safety factor should be retained (Tarplee, DOC # 014272). The Committee recommended that the **FQPA safety factor** be **reduced** to 3x because: 1) the toxicology data base is complete; 2) the available data provide no indication of quantitative or qualitative increased susceptibility in rats from *in utero* exposure to lindane in the prenatal developmental study; 3) although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a new study is not required (See Section I.B.); 4) the offspring effects seen in the developmental neurotoxicity study were the same as those seen in the two-generation reproduction study; and 5) adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment; and 6) there are currently no residential uses.

ii. Cancer Classification

On May 30, 2001, the HED Cancer Assessment Review Committee (CARC) met to evaluate the carcinogenic potential of lindane. At this meeting, the CARC could not make a determination of the carcinogenic potential of lindane because the NTP studies were of limited value and it was uncertain if the study on Agouti, Pseudoagouti and Black mice with limited data could be used for regulatory purposes. In addition, the CARC was informed that new histopathology data would be submitted. The Committee also requested additional information including results of a 90-day subchronic range-finding study in CD-1 mice, an earlier RfD Committee report and analyses of the older studies on lindane.

The Committee met again on September 13, 2001 and reevaluated all the available information/data including the old and the newly gathered information that was previously not available for review. Based on the most recent review of the data including the newly submitted carcinogenicity study in CD-1 mice and in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC has classified lindane into the category **"Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"** based on an increased incidence of benign lung tumors in female mice only. The Committee, therefore, recommended that the quantification of human cancer risk is not required.

iii. Toxicology Endpoint Selection

The Hazard Identification Committee (HIARC) met on June 13, 2000 to evaluate the existing toxicology database for lindane and identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and durations, and assess/reassess the reference dose (RfD). HIARC met again on May 22, 2001 to reconsider the endpoint for occupational risk assessment for the inhalation route of exposure. Previously the endpoint was based on kidney lesions and increased kidney weights resulting from the accumulation of alpha 2μ globulin. These effects have been deemed not relevant for human risk assessment. The conclusions and toxicology endpoints selected for dietary and non-dietary risk assessments are presented in Table 3 below.

The critical toxicology study for acute dietary risk assessment is the acute neurotoxicity study in rats. In an acute oral neurotoxicity study, groups of 10 rats/sex/dose were administered a single dose of lindane by gavage at concentrations of 0 (control), 6, 20, or 60 mg/kg. Functional
observational battery (FOB) and motor activity (MA) testing were performed prior to administration and within 3 hours (time of peak effect) of dosing (day 0), and on days 7 and 14 post-dose. Body weights were recorded pre-test, weekly during the study period and on FOB assessment days. Clinical signs were recorded at least once daily. At study termination all animals were sacrificed and fixed by whole body perfusion, designated tissues of the nervous system were processed for microscopic neuropathological evaluation. The NOAEL for

neurotoxic effects was found to be 6 mg/kg for females and the LOAEL was 20 mg/kg based on increased forelimb grip strength and decreased grooming behavior and motor activity (MA). The NOAEL for neurotoxicity in males is 20 mg/kg and the LOAEL for males is 60 mg/kg based on tremors, convulsions, decreased MA, and increased forelimb grip strength. The Uncertainty Factor includes 10x for inter-species variation, and10X for intra-species extrapolation. The FQPA safety factor is reduced to 3X. **Therefore, the acute Population Adjusted Dose (aPAD) is 0.02 mg/kg/day (NOAEL of 6 mg/kg/day ÷ 300 (UF of 100 x FQPA factor of 3).**

The acute dietary endpoint for the general population was considered sufficiently protective for the subpopulation of females 13-50. Although, there was evidence of increased susceptibility in the DNT, the offspring effects were not attributable to a single dose. A separate endpoint for this subpopulation was therefore not identified.

The critical toxicology study for chronic non-cancer dietary risk assessment is the chronic toxicity/oncogenicity study in rats. In this chronic toxicity/oncogenicity study, lindane was administered in the diet to groups of 115 male and 115 female Wistar rats per dose at concentrations of 0, 1, 10, 100, or 400 ppm for 2 years. Corresponding delivered doses were 0, 0.05, 0.47, 4.81, and 19.66 mg/kg/day, respectively, for males and 0, 0.06, 0.59, 6.00, and 24.34 mg/kg/day, respectively, for females. The systemic toxicity LOAEL for male and female rats is 100 ppm (4.81 and 6.0 mg/kg/day, respectively) based on periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets. The systemic toxicity NOAEL is 10 ppm (0.47 and 0.59 mg/kg/day for males and females, respectively). The Uncertainty Factor includes 10X for inter-species variation, and10x for intra-species extrapolation. The FQPA safety factor is reduced to 3X.. **Therefore, the chronic Population Adjusted Dose (cPAD) was determined to be 0.0016 mg/kg/day (NOAEL of 0.0047 mg/kg/day ÷ 300 (UF of 100 x FQPA of 3).**

For occupational assessment, the dermal absorption rate for lindane was estimated to be approximately 10% in 10 hours of exposure in humans. The HIARC concurred with the TES committee decision (HED Doc. # 013460) that the dermal absorption factor is 10% based on a published report by Feldman and Maibach (Toxicology and Applied Pharmacology 28, 126-132, 1974).

Table 3. Doses and Toxicological Endpoints Selected for Risk Assessment of Lindane

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY TYPE/ MRID
Acute Dietary- general population	NOAEL= 6 mg/kg UF = 100	LOAEL is 20 mg/kg based on increased grip strength, increased motor activity	Acute Neurotoxicity in Rats/ 44769201
Acute RfD = 0.06 mg/kg/day		**aPAD = 0.02 mg/kg/day**	

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY TYPE/ MRID
Chronic Dietary	NOAEL= 0.47 mg/kg/day UF = 100	LOAEL is 100 ppm (4.81 mg/kg/day) periacinar hepatocyte hypertrophy, increased liver/spleen weight, increased platelets	Chronic Feeding and Carcinogenicity in Rats 41094101, 41853701 42891201
Chronic RfD = 0.0047 mg/kg/day cPAD = 0.0016 mg/kg/day			
Short-Term [1] (Dermal)	NOAEL= 1.2 mg/kg/day	LOAEL is 50 ppm based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.	Developmental Neurotoxicity Study in Rats 45073501
Intermediate-Term [1] (Dermal)	NOAEL= 1.2 mg/kg/day	LOAEL is 50 ppm based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.	Developmental Neurotoxicity Study in Rats 45073501
Long-Term [1] (Dermal)	NOAEL= 0.47 mg/kg/day	LOAEL is 100 ppm (4.81 mg/kg/day) periacinar hepatocyte hypertrophy, increased liver/spleen weight, increased platelets	Chronic Feeding and Carcinogenicity in Rats 41094101, 41853701 42891201
Dermal Absorption Factor = 10%			
Short Term [1] (Inhalation)	0.13 mg/kg/day (0.5 mg/m^3)	based on clinical signs (diarrhea, piloerection) seen at day 14 and continuing for 20 days	90-Day Inhalation Toxicity / 00255003
Intermediate Term [1] (Inhalation)	0.13 mg/kg/day (0.5 mg/m^3)	LOAEL is 5.0 mg/m^3 based on increased kidney weights of female rats and bone marrow effects.	90-Day Inhalation Toxicity / 00255003
Long Term [2] (Inhalation)	N/A	N/A	N/A

[1] An MOE of 100 was selected

[2] Exposure thru this route for this duration is not expected

The Maibach study tested 12 pesticides and herbicides, including lindane, on human subjects (6 per chemical) to quantify their dermal penetration. C^{14}-labeled chemicals were applied topically (4μg/cm^2) to the forearm or via the intravenous route (1μCi). Excretion of the chemicals was then monitored by collecting and analyzing urine samples during the 5 day testing period. All results were calculated as percent of the injected or applied dose. Data obtained after IV dosing was used to correct the skin penetration data for incomplete urinary recovery. Lindane was shown to have a penetration factor of 9.3% ± 3.7 (SD).

The critical study selected for short- and intermediate-term dermal risk assessment was the Developmental Neurotoxicity Study in rats. A 90-day dermal toxicity study in rabbits was available; the NOAEL was 10 mg/kg/day and the LOAEL was 60 mg/kg/day based on hepatic toxicity. The HIARC did not consider this study to be appropriate for risk assessment and instead selected an oral endpoint due to: 1) the concern for developmental effects as seen in pups

in the developmental neurotoxicity study, 2) developmental effects are not evaluated in the dermal toxicity study, 3) the dermal toxicity study was conducted in the rabbit, while the increased susceptibility was seen in rat pups via an oral route, and 4) this endpoint will be protective of dermally exposed workers. For developmental toxicity, the NOAEL was 1.2 mg/kg/day and the LOAEL was 5.6 mg/kg/day based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation. The target MOE is 100 (10X for interspecies variation and 10X for intraspecies variation) for occupational exposure. Since an oral endpoint was selected, a 10% dermal absorption factor will be used for route to route extrapolation.

The critical study selected for risk assessment for long-term dermal exposure was the Chronic One-Year Toxicity Study in rats, which is discussed above. The systemic toxicity LOAEL for male and female rats is 4.81 and 6.0 mg/kg/day, respectively, based on periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets. The systemic toxicity NOAEL is 0.47 and 0.59 mg/kg/day for males and females, respectively. The target MOE is 100 (10X for interspecies variation and 10X for intraspecies variation) for occupational exposure. Since an oral endpoint was selected, a 10% dermal absorption factor will be used for route to route extrapolation.

The critical study for inhalation risk assessment for lindane is an 90-Day Inhalation Toxicity. Lindane was administered by inhalation to groups of 12 male and 12 female Wistar rats at nominal concentrations of 0, 0.02, 0.10, 0.50, or 5.0 mg/m^3, 6 h/day for 90 days. Lindane was detected in the brain, liver, fat, and serum of all exposed rats. The HIARC established a NOAEL of 0.5 mg/m^3 for this risk assessment based on clinical signs (diarrhea and piloerection) seen at day 14 after exposure and continuing for 20 days at the highest concentration tested (5 mg/m^3). This NOAEL is applicable and appropriate only for short-term exposure risk assessment because the effects were seen during this period of exposure. For intermediate exposures, the NOAEL is 0.5 mg/m^3 (0.13 mg/kg) based on increased kidney weights and bone marrow effects. For inhalation risk assessments for occupational exposure, the target MOE is 100 (10X for intraspecies variation and 10X for interspecies variation). Long-term inhalation exposure is not expected.

iv. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that

effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

v. Incident Reports

The Agency has conducted a review of reported poisoning incidents associated with human exposure to lindane. The Agency has consulted the following data bases for the poisoning incident data on the active ingredient lindane: Incident Data System, Poison Control Center Data - 1993 through 1998, California Data - 1982 through 1998, and the National Pesticide Telecommunications Network.

The review only included lindane containing products currently registered for use as a seed treatment. Incidents due to all other types of lindane products were excluded. No incidents were located related to seed treatment use of lindane. None of the cases reported to Poison Control Centers from 1993 through 1998 concerned products identified as being used for seed treatment. However, it should be noted that nearly one-third of the exposures involving lindane did not identify a specific product, but rather just exposure to lindane. Detailed descriptions of eight cases submitted to the California Pesticide Illness Surveillance Program (1982-1998) were reviewed. In three of these cases, lindane was deemed the primary cause of the illness. All three incidents occurred in 1984. All three cases involved driving and filling planter hoppers with treated cotton seed. Two of the cases, apparently involved in the same operation, were both treated in a hospital and off work for 7 days. The third case was not treated in a hospital but was off work for 2 days. Specific symptoms were not reported for any of these three cases. The National Pesticide Telecommunications Network did not report on incidents specifically related to lindane use for seed treatment. Relatively few incident of illness have been reported due to lindane used for seed treatment; therefore, no recommendations can be made based on the few incident reports available.

IV. Exposure and Risk Assessment

A. Dietary Exposure (Food Sources)

i. Background

In 1993, CIEL offered to voluntarily cancel all crop uses of lindane except seed treatment and certain non-food uses. The Agency considers lindane seed treatment as a food use requiring tolerances based on existing data from radiolabeled studies indicating uptake of residues from the treated seeds into the aerial portion of the growing crop.

The only food/feed use of lindane which is being supported for reregistration is seed treatment on canola, spinach, and cereal grains (excluding rice and wild rice). Seed treatment

uses on broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, radishes, and spinach are no longer being supported for reregistration by Inquinosa. In addition, the established tolerances for the following commodities will be revoked because no registrants have committed to support the foreign or domestic uses for: apples, apricots, asparagus, avocados, celery, cherry, collards, cucumbers, eggplants, grapes, guavas, kale, kohlrabi, mangoes, melons, mushrooms, mustard greens, nectarines, okra, onions (dry bulb only), peaches, pears, pecans, peppers, pineapple, plums (fresh prunes), pumpkins, quinces, squash, strawberries, summer squash, swiss chard and tomatoes.

Tolerances for residues of lindane in/on food and feed commodities are currently established under 40 CFR §180.133 and are expressed in terms of lindane *per se*. The nature of the residue in plants and ruminants is not adequately understood. New nature of the residue studies from seed treatment are required for a cereal grain, leafy vegetable, and radish. Additional data are required for the ruminant metabolism study. The nature of the residue in poultry is adequately understood. The HED Metabolism Assessment Review Committee (T. Morton, 8/30/00, D267069) concluded that the TRRs should be used for risk assessment purposes and calculation of dietary burdens, pending receipt of additional metabolism data.

Table 4. Tolerance Reassessment Summary for Lindane.

Commodity	Tolerance Listed Under 40 CFR (ppm)	Reassessed Tolerance (ppm)	Comment *[Correct Commodity Definition]*
Tolerance Listed Under 40 CFR §180.133			
Apples	1	Revoke	Not being supported for reregistration.
Apricots	1	Revoke	Not being supported for reregistration.
Asparagus	1	Revoke	Not being supported for reregistration.
Avocados	1	Revoke	Not being supported for reregistration.
Broccoli	1	Revoke	Not being supported for reregistration.
Brussels sprouts	1	Revoke	Not being supported for reregistration.
Cabbage	1	Revoke	Not being supported for reregistration.
Cauliflower	1	Revoke	Not being supported for reregistration.
Lettuce	3	Revoke	Not being supported for reregistration.
Spinach	1	Revoke	Not being supported for reregistration.
Celery	1	Revoke	Not being supported for reregistration.
Collards	1	Revoke	Not being supported for reregistration.
Kale	1	Revoke	Not being supported for reregistration.
Kohlrabi	1	Revoke	Not being supported for reregistration.
Mustard greens	1	Revoke	Not being supported for reregistration.
Swiss chard	1	Revoke	Not being supported for reregistration.
Cherry	1	Revoke	Not being supported for reregistration.
Cucumbers	3	Revoke	Not being supported for reregistration.
Eggplants	1	Revoke	Not being supported for reregistration.

Table 4 (*continued*).

Commodity	Tolerance Listed Under 40 CFR (ppm)	Reassessed Tolerance (ppm)	Comment *[Correct Commodity Definition]*
Fat of meat from cattle, goats, horses, and sheep	7	To be determined (TBD)	The Agency will re-calculate the maximum theoretical dietary burden for livestock animals and re-assess the adequacy of the available animal feeding studies when the requested residue data for livestock feed items have been received and evaluated.
Fat of meat from hogs	4		
Grapes	1	Revoke	Not being supported for reregistration.
Guavas	1	Revoke	Not being supported for reregistration.
Mangoes	1	Revoke	Not being supported for reregistration.
Melons	3	Revoke	Not being supported for reregistration.
Mushrooms	3	Revoke	Not being supported for reregistration.
Nectarines	1	Revoke	Not being supported for reregistration.
Okra	1	Revoke	Not being supported for reregistration.
Onions (dry bulb only)	1	Revoke	Not being supported for reregistration.
Peaches	1	Revoke	Not being supported for reregistration.
Pears	1	Revoke	Not being supported for reregistration.
Pecans	0.01	Revoke	Not being supported for reregistration.
Peppers	1	Revoke	Not being supported for reregistration.
Pineapple	1	Revoke	Not being supported for reregistration.
Plums (fresh prunes)	1	Revoke	Not being supported for reregistration.
Pumpkins	3	Revoke	Not being supported for reregistration.
Quinces	1	Revoke	Not being supported for reregistration.
Squash	3	Revoke	Not being supported for reregistration.
Strawberries	1	Revoke	Not being supported for reregistration.
Summer squash	3	Revoke	Not being supported for reregistration.
Tomatoes	3	Revoke	Not being supported for reregistration.
Tolerance To Be Proposed Under 40 CFR §180.133			
Barley, grain	None established	TBD	A nature of the residue study for lindane residues resulting from seed treatment application to a cereal grain is required.
Barley, hay		TBD	
Barley, straw		TBD	
Canola, seed		TBD	
Corn, grain		TBD	
Corn, forage		TBD	
Corn, stover		TBD	
Oat, grain		TBD	
Oat, forage		TBD	
Oat, hay		TBD	
Oat, straw		TBD	

Table 4 (*continued*).

Commodity	Tolerance Listed Under 40 CFR (ppm)	Reassessed Tolerance (ppm)	Comment *[Correct Commodity Definition]*
Rape greens		TBD	
Rye, grain		TBD	
Rye, forage		TBD	
Rye, straw		TBD	
Sorghum, grain		TBD	
Sorghum, forage		TBD	
Sorghum, stover		TBD	
Wheat, grain		TBD	
Wheat, forage		TBD	
Wheat, hay		TBD	
Wheat, straw		TBD	

TBD = To be determined.

ii. Sources of Lindane Residues on Foods

The only food/feed use of lindane which is being supported for reregistration is seed treatment on canola, spinach, and cereal grains (excluding rice and wild rice). Seed treatment uses on broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, radishes, and spinach are no longer being supported for reregistration. There are no adequate nature of the residue studies for plants from seed treatment application; therefore, new metabolism studies are required for cereal grain. A seed treatment metabolism study was reviewed by HED; although it was deemed inadequate due to insufficient characterization/ identification of the radioactive residues, it was found to be useful in the determination of the TRR for use in this dietary exposure analysis. The corn grain and forage TRRs were translated to sorghum. The nature of the residue in poultry is understood. The nature of the residue in ruminants is adequately understood since the registrant recently submitted the required data (MRID 45224101, 45224102, and 45277201) to upgrade a ruminant metabolism study (MRID 44867104) which was deemed inadequate. The lindane equivalent residue values used in the dietary exposure analyses were derived using a ratio of total radioactive residue divided by the amount of lindane present in the metabolism studies (ruminant and poultry). This would be worst case estimate since we are assuming that all of the TRR would be residues of concern.

The dietary exposure analyses using the total radioactive residues is a Tier 3 assessment since percent crop treated was used in the analyses. The dietary exposure analyses that were based on the adjustment of the lindane residues in the livestock feeding studies is a Tier 3 assessment. Percent market share was available for all crops included in the analyses. Since lindane is registered for seed treatments only, there is no difference in the percent crop treated between crops grown for the fresh market and those grown for processing. A processing study

was available for canola only; the default DEEM™ processing factors were used for all other foods.

iii. Residue Chemistry Studies for Lindane

A tabular summary of the residue chemistry science assessments for reregistration of lindane is presented in Table A of the Revised Residue Chemistry Chapter (T. Morton, D279259, 12/11/01). When end-use product DCIs are developed (e.g., at issuance of the RED), all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) should be amended such that they are consistent with the basic producers' labels. A 30-day plant-back interval for leafy vegetables and a 12-month plant-back interval for all other unregistered crops is required on all end-use product labels for lindane.

Nature of the Residue - Plants (GLN 860.1300):

The qualitative nature of lindane residues in plants reflecting seed treatment is inadequately understood. For the purpose of reregistration, the basic registrants are required to conduct new plant metabolism studies on lindane. These studies should be conducted on a representative cereal grain, as the registrants have indicated that the only food uses they are supporting are for seed treatment of these crops. The new studies should be conducted at rates which insure that sufficient ^{14}C-residues are available for analysis. Crop samples should be harvested at the appropriate stage. Identification of ^{14}C-residues should also be confirmed using more than one method, or by GC/MS.

Nature of the Residue - Animals (GLN 860.1300):

No direct livestock treatments remain registered. Residues of lindane may occur in livestock as a result of feeding on lindane treated feed (secondary residues). The qualitative nature of the residue in ruminants is adequately understood. The basic registrants have recently submitted additional data for the ruminant metabolism study (MRID 44867104) which was deemed inadequate but upgradable. To upgrade the study, the registrant was required to identify the metabolite labeled LiV in goat liver's aqueous phase which accounted for 25.2 % of the total radioactivity (0.57 ppm). In addition, storage stability data was required. The registrant has recently submitted the required data (MRID 45224101, 45224102, and 45277201) thus, adequately addressing this deficiency. The total radioactive residues (TRR; expressed as lindane equivalents) in collected samples were 3.46 ppm in fat, 2.25 ppm in liver, 0.48 ppm in kidney, 0.20 ppm in muscle, and 0.20 ppm in milk. The parent, lindane was the major residue identified in all goat matrices.

The qualitative nature of the residue in poultry is adequately understood. A poultry metabolism study (MRIDs 40271301 and 44405404), submitted by the registrants in response to the 9/85 Lindane Reregistration Guidance Document, has recently been upgraded to acceptable status. A brief summary of the poultry metabolism study follows. Laying hens were dosed with [^{14}C]lindane at levels equivalent to 1.2 ppm or 120 ppm in the diet for four consecutive days. Radioactive residues accumulated to the greatest extent in fatty tissues. In high dose hens, TRR

levels were highest in fat (96.98 ppm) and lowest in breast muscle (1.44 ppm). TRR levels were proportionally less in tissues of low-dose hens (fat, 1.26 ppm; breast muscle 0.02 ppm). In eggs of high-dose hens, ^{14}C-residues peaked on Day 4 at 10.83 ppm in yolks and 0.21 ppm in whites. Lindane was the major residue component identified and accounted for approximately 95% of the TRR in egg yolks, 71-86% of the TRR in muscle, skin, and fat, and 52% of the TRR in liver. Other metabolites that were identified included: 1,2,4-trichlorobenzene; 1,3,5-trichlorobenzene and dichlorobenzene(s); tetrachlorobenzene (either 1,2,4,5- or 1,2,3,4-); PCCH; 1,2,3,4-tetrachlorobenzene/tetrachlorocyclohexene; 1,2,3,4,5-pentachlorobenzene; and hexachlorocyclohexene.

The results of the ruminant and poultry metabolism studies will be presented to HED's MARC for determination of terminal residue of concern in eggs, milk, and animal tissues once adequate seed treatment metabolism studies are submitted. If the Committee determines that lindane is the only residue of concern requiring regulation, then the existing storage stability data for poultry commodities, the analytical method used for data collection, and the poultry feeding study will be upgraded to acceptable status.

In the absence of acceptable metabolism studies, the HED MARC (T. Morton, 8/30/00, D267069) concluded that the total radioactive residues should be used for risk assessment purposes until adequate plant metabolism studies are submitted.

Residue Analytical Methods (GLN 860.1340):

Adequate methods are available for determination of residues of lindane *per se* in/on plant and animal commodities. The Pesticide Analytical Manual (PAM) Vol. II lists Methods I and II for the analysis of mixed isomers of 1,2,3,4,5,6-hexachlorocyclohexane in/on plant and animal commodities. Method I is a multiresidue method (see "GLN 860.1360: Multiresidue Methods" section) for chlorinated compounds. Method II is based upon the official final AOAC method (1990, 15th edition of AOAC) and is suitable for determining residues of lindane in/on AOAC Group I nonfatty foods (vegetables and fruits), dairy products, fish, and eggs. The stated limit of detection of Method II is 0.05 ppm for most commodities.

Because the nature of the residue in plants resulting from seed treatment uses as well as the nature of the residue in ruminants have not been delineated, the adequacy of the available analytical methods cannot be determined. The registrants are reminded that radiovalidation of enforcement method(s) is a reregistration requirement; therefore, representative samples from the requested plant and ruminant metabolism studies should be used for validation and analyzed by the existing or proposed enforcement method(s) to determine whether total toxic residues are extracted from weathered samples.

Adequate data-collection methods have been submitted for detection of lindane *per se* in/on cucumbers and spinach. The analytical procedures for detecting lindane in cucumbers and spinach are essentially the same. Based on acceptable method validation recoveries, the Agency has deemed the GC/ECD method to be adequate for determining residues of lindane *per se* in nonfatty crops.

A GC/MS method (SOP# Meth-109) entitled "Determination of Lindane in Wheat and Canola Matrices" was utilized as the data-collection method in a recently submitted wheat field study. Following extraction and purification, detection and quantitation were conducted using a gas chromatograph equipped with a mass selective detector (GC/MS). The LOQ was 0.005 ppm.

A data-collection method, based on the AOAC method, was also submitted for detection of lindane *per se* in eggs, milk, and animal tissues. The Agency previously required an EPA method validation for the submitted method if lindane tolerances for lean animal tissues were to be established because the AOAC method did not describe techniques which the registrant's method contained (e.g., gel permeation chromatography and rotary evaporation). The FDA method now utilizes these techniques; therefore, the requirement for a petition method validation was conditionally waived provided HED's MARC determines that lindane *per se* is the only residue of concern in animal commodities.

Multiresidue Methods (GLN 860.1360):

The 10/99 PESTDATA database (PAM, Vol. I, Appendix I) contains data concerning the applicability of multiresidue methods to lindane. Lindane is completely recovered (>80% recovery) using protocols 302 (Luke method), 303 (Mills, Onley, and Gaither method), and 304 (Mills method) for fatty and non-fatty foods. Should the HED MARC determine that lindane metabolites other than the parent should be regulated, the Agency will require the registrants to submit additional multiresidue methods test data for the metabolites of concern.

Storage Stability Data (GLN 860.1380):

The specifics of reregistration requirements for storage stability data in plants and animals cannot be ascertained until acceptable plant metabolism studies are available, and the HED MARC has determined the terminal residues of concern. Assuming that lindane *per se* is the terminal residue of concern and provided the additional temperature information is submitted, the available storage stability data for lindane support the storage conditions and intervals of samples collected from existing crop field trials and livestock feeding studies. A summary of available storage stability data for lindane *per se* is summarized below.

Raw agricultural and processed commodities: Residues of lindane *per se* are relatively stable under frozen (-20° C) storage conditions for up to 8 months in/on cucumbers and spinach and for approximately 14 months in/on tomatoes and wheat forage. Lindane residues are stable in wheat grain, wheat hay, and wheat straw for approximately 18 months when stored under frozen conditions. Lindane residues in canola seed were stable for up to 6.5 months when stored under frozen conditions (no temperature given). Lindane residues were stable for up to 2 months in canola oil and 1.5 months in canola meal when stored under frozen conditions (no temperature given). The registrant is required to submit additional storage stability data (temperature logs) specifying the storage conditions of the canola storage stability samples. Assuming that lindane *per se* is the terminal residue of concern, these data support the storage conditions and intervals of samples collected from existing crop field trials.

Animal commodities: Residues of lindane *per se* are relatively stable in eggs, milk, and edible tissues of animals stored frozen (-18° C) for up to 9 months. Assuming that lindane *per se* is the terminal residue of concern, these data support the storage conditions and intervals of samples collected from existing ruminant and poultry feeding studies.

Crop Field Trials (GLN 860.1500):

A translocation study (MRID 40431207) formed the basis for food-use classification of lindane when the pesticide is applied as a seed treatment. In this study, [^{14}C]lindane was applied as a seed treatment to corn (field and sweet), mustard, radish, spinach, sugar beet, and wheat at approximately 1x the label rate. The treated seeds were then planted outdoors in 55 gallon drum halves and allowed to grow under simulated normal agricultural practices. Samples of immature and mature crop commodities were analyzed for total ^{14}C, and some fractions were extracted with hexane and analyzed by a GC method for total lindane. The study failed to adequately identify radioactive residues in/on all commodities grown from treated seed. Nonetheless, with the possible exception of wheat grain and foliage, residues were characterized to be not associated with biological molecules (e.g., amino acid, sugar, etc.) that have incorporated the radiolabel. Should the HED MARC determine that lindane metabolites other than the parent should be regulated, the Agency will require the registrants to submit additional crop field trial data for all residues of concern.

The registrants have submitted PP#9F05057, for the establishment of time-limited tolerances for residues of lindane *per se* in/on the RACs of crops for which seed treatments are being proposed. Tolerances cannot be established or reassessed until adequate plant metabolism studies are submitted.

The registrants have also submitted PP#9F6022, for the establishment of tolerances on lindane *per se* in/on canola for which seed treatment is being proposed. Tolerances cannot be established or reassessed until adequate plant metabolism studies and additional residue data are submitted.

In addition, the registrants recently submitted acceptable residue data reflecting seed treatment on wheat RACs. A representative formulation (lindane 30-C flowable) was applied as a seed treatment to wheat at 0.52 oz. ai/cwt (or 330 ppm lindane on the seed). Following treatment, the treated seeds were planted in 15 diverse geographic locations. Wheat forage samples were collected at or near the jointing stage, the hay samples at early flower to soft dough stage, and the grain and straw samples at normal harvest maturity. Residues of lindane were nondetectable (<0.005 ppm) in/on all treated wheat grain and straw samples. Residues of lindane ranged from <0.005 ppm (nondetectable) to 0.04 ppm in/on treated wheat forage and from <0.005 ppm (nondetectable) to 0.02 ppm in/on treated wheat hay. Additional residue data would be required if the HED MARC determines residues of concern include metabolites of lindane in addition to lindane *per se*.

Processed Food/Feed (GLN 860.1520):

No data are available to determine whether lindane residues of concern concentrate in the processed fractions of cereal grains following seed treatment. A processing study on corn is required for the purpose of reregistration. A processing study on wheat would also be required if the HED MARC determines residues of concern include metabolites of lindane in addition to lindane *per se*.

At this time, a processing study for wheat processed fractions is not being required if lindane *per se* is the only residue of concern (S. Funk, 10/31/95, D213401). In 1998, the U.S. Food and Drug Administration (FDA) monitoring program analyzed a total of 227 samples of milled grain products for lindane residues at an LOQ of 0.01 ppm. Commodities analyzed included flour and other milled products, breakfast foods, and baked goods. Lindane was not detected in any sample.

The registrant submitted a canola processing study along with PP#9F6022 where lindane residues in/on canola refined oil, canola meal, and bleached/deodorized canola oil were determined. Lindane in canola refined oil concentrated by a factor of at least 5.2x. Lindane did not concentrate in canola meal and bleached/deodorized canola oil.

Meat, Milk, Poultry, Eggs (GLN 860.1480):

The nature of the residue in plants is not understood. Upon receipt of the requested plant metabolism data, the Agency will: (i) determine the adequacy of established tolerances for animal commodities; (ii) calculate the expected dietary intake for beef cattle, dairy cattle, and swine; and (iii) re-evaluate the need for additional feeding studies.

It should be noted that ruminant (M. Kovacs, 9/20/88, CB No. 4037) and poultry feeding (G. Otakie, 8/31/88, RCB No. 4034) studies are available assuming that lindane *per se* is the only residue of concern in animals.

Confined/Field Accumulation in Rotational Crops (GLN 860.1850 and 860.1900):

The basic registrants have submitted a confined rotational crop study which was deemed unacceptable and not upgradable because of inadequate characterization and identification of residues due to significant losses of organosoluble residues during analysis. Although the study is inadequate and the application rate used (0.75 lb ai/A) greatly exceeds the level of soil residues that are likely to result from seed-treatment uses, the data indicate that residues of lindane persist in the soil and can be taken up by rotational crops at intervals up to one year.

For the purpose of reregistration, the Agency will not require a new confined rotational crop study provided the registrants propose a 30-day plantback interval for leafy vegetables and a 12-month plantback interval for all other unregistered crops on all end-use product labels for lindane as recommended by the ChemSAC (memo, 10/5/00). Since this proposal has been accepted by the registrants, then limited rotational field trial data will not be required.

B. Dietary Exposure Estimates

The Agency conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, the entire distribution of single day food consumption events is combined with either a single residue level (deterministic analysis, risk at 95th percentile of exposure reported) or a distribution of residues (probabilistic analysis, referred to as "Monte Carlo," with level of concern at 99.9th percentile of exposure reported) to obtain a distribution of exposures in mg/kg/day. For chronic dietary risk assessments, the three-day average of consumption for each sub-population is combined with average residues in/on commodities to determine an average exposure in mg/kg/day. For lindane, the acute dietary exposure analysis was a tier 3 probabilistic assessment.

Seed treatment uses on broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, radishes, and spinach are no longer being supported for reregistration by Inquinosa. Therefore, revised acute, chronic dietary exposure and risk analyses have been conducted with these commodities removed (T. Morton, 12/13/01, 279260). The HED Metabolism Assessment Review Committee (T. Morton, 8/30/00, D267069) concluded that the TRRs should be used for risk assessment purposes and calculation of dietary burdens, pending receipt of additional metabolism data. The HED ChemSAC recommended comparing the results from the dietary exposure analysis using the TRRs as the residue input with results from a second dietary exposure analysis using lindane residues per se from the livestock feeding studies. Exposure to lindane was determined by using the ratio (ppm TRR/ppm lindane parent) from the livestock metabolism studies. Only the commodities being supported by the registrant were included in the dietary exposure analysis; no import uses were included as all of these tolerances will be revoked. Additionally, FDA monitoring data show that residues of lindane are not being found in imported commodities. Some residues are reported for γ–BHC but these residues are associated with use of BHC, not lindane. The Biological and Economic Analysis Division (OPP/BEAD) verified the registrant's percent market share estimate for lindane (I. Yusuf email, 7/17/00). A canola processing study for lindane was recently reviewed (T. Morton, D269388, 5/10/01). Lindane was not detected in bleached/deodorized canola oil (<0.005 ppm). Therefore, ½ LOQ (0.0025 ppm) will be used as the DEEM™ adjustment factor 1. DEEM™ default concentrations factors (adjustment factor 1) will be used for all other concentration factors. The wheat grain and forage TRRs were translated to barley, oats, and rye. The corn grain and forage TRRs were translated to sorghum.

Anticipated residues (DP Barcode D279260, T. Morton, 12/4/01) were provided for all commodities and have been used when calculating the dietary risk. Although the database for lindane is substantially complete, additional data are needed to eliminate the uncertainties associated with the exposure/risk assessment. The anticipated residue values are the best estimates the Agency can provide using the residue data available at this time. These values have an inherent uncertainty associated with variations in analytical methods, geographical representation of field trials, seasonal variation of residue levels, etc.

C. Dietary Risk Estimates (Food Sources)

The only food/feed use of lindane which is being supported for reregistration is seed treatment on canola, spinach, and cereal grains (excluding rice and wild rice). Seed treatment uses on broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, radishes, and spinach are no longer being supported for reregistration. A revised DEEM™ analysis was performed to estimate acute and chronic dietary exposure and risk from lindane from all commodities supported for reregistration, i.e., seed treatment of canola, spinach, and cereal grains (T. Morton, 12/13/01, D279260). The HED Metabolism Assessment Review Committee concluded that the TRRs should be used for risk assessment purposes and calculation of dietary burdens, pending receipt of additional metabolism data (T. Morton, D267069, 8/30/00).

Table 5. Estimated Acute and Chronic Dietary Exposure and Risk using the feeding studies and adjusting lindane residues using the metabolism studies.

Population Subgroup	Acute (99.9th %-ile)		Chronic	
	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	% cPAD
U.S. Population	0.001305	7	0.000054	3
All infants (<1 yr)	0.003320	17	0.000072	5
Children (1-6 yrs)	0.001973	10	0.000173.	11
Children (7-12 yrs)	0.001088	5	0.000096	6
Females (13-50 yrs)	0.000467	2	0.000034	2
Males (13-19 yrs)	0.000670	3	0.000061	4
Males (20+ yrs)	0.000458	2	0.000034	2
Seniors (55+ yrs)	0.000409	2	0.000030	2

i. Acute Dietary Exposure and Risk Estimates

Estimated acute dietary exposure is below HED's level of concern for all population subgroups at the 99.9th percentile. The maximum dietary risk estimate is 17 % of the acute PAD (% aPAD) for the population subgroup All Infants (Table 5) and 7 % of the aPAD for the U.S. Population when the feeding studies were adjusted using the metabolism studies.

ii. Chronic Dietary Exposure and Risk Estimates

Estimated chronic dietary risk is below HED's level of concern. The resulting risk estimates are 3 % of the chronic PAD (% cPAD) for the U.S. Population and 11 % of the cPAD

for Children 1-6 years of age (the most highly exposed population subgroup. The remaining population subgroups were <6 % of the cPAD (Table 5) when the feeding studies were adjusted using the metabolism studies.

iii. Chronic Dietary Exposure and Risk Estimates for Indigenous People

The Indigenous Peoples of the Arctic region of the U.S. (Alaska) rely heavily on subsistence diets as their food source. HED performed a revised supplementary chronic dietary risk and exposure assessment to assess the risk to Indigenous People from worldwide use and manufacture of lindane (T. Morton, D280076, 1/8/02). Because the annual harvest rates were divided by 365 to obtain daily harvest rates, and the daily intake rates used in the assessment no acute dietary exposure analysis was conducted. The chronic analysis used subsistence food harvest amounts, total HCH residues in traditional foods, and adjusting the HCH exposure to obtain lindane exposure. Based on revised exposure estimates, the chronic dietary risk to adult male Indigenous People ranges from 0.000055 - 0.0006 mg/kg body weight/day which is between 3 and 38 % of the cPAD. This is below HED's level of concern (cPAD = 0.0016 mg/kg bw/day). The revised estimate of chronic dietary risk to adult female Indigenous People ranges from 0.000064 - 0.0007 mg/kg bw/day or from 4 to 44 % of the cPAD, also below HED's level of concern. The revised lindane dietary risk estimates for children resulting from subsistence food consumption range from 0.0002 - 0.0022 mg/kg bw/day or from 13% to 138% of the cPAD.

Table 6. Assumed Total Dietary Intake of Lindane (gamma-HCH) and Estimated Chronic Dietary Risk for Indigenous Peoples

Population Subgroup	Body Weight (kg)	Lindane Exposure (mg/kg/day)	% cPAD
Adult male	70	0.000055 - 0.0006	3-38
Adult female	60	0.000064 - 0.00071	4-44
Children	10	0.0002 - 0.0022	13-138

iv. Cancer Dietary Risk Estimates

No dietary cancer risks for lindane were estimated.

D. Uncertainties in Dietary Exposure Assessment

There are no adequate nature of the residue studies for plants from seed treatment application. New metabolism studies are required for three crops; however, a seed treatment metabolism study (which was classified as inadequate) was reviewed by the Agency and used in the determination of the TRR for use in this dietary exposure analysis. The mustard foliage TRR was translated to broccoli, Brussels sprouts, cabbage, cauliflower, radish tops, and lettuce. The wheat grain and forage TRRs were translated to barley, oats, and rye. The corn grain and forage TRRs were translated to sorghum. The nature of the residue in poultry and ruminants is understood. The magnitude of the residue studies in poultry and cattle only analyzed for lindane.

The total residue equivalents values were derived using a ratio of total radioactive residue divided by the amount of lindane present in the metabolism studies. This would be worst case estimate since we are assuming that all of the TRR would be residues of concern.

The dietary exposure analyses using the total radioactive residues is a Tier 3 probabilistic assessment since percent crop treated was used in the analyses. Percent market share was available for all crops included in the analyses. Since lindane is registered for seed treatments only, there is no difference in the percent crop treated values between crops grown for the fresh market and those grown for processing. A processing study was available for canola only; the default DEEM™ processing factors were used for all other foods.

E. Drinking Water Exposure

Although the only current agricultural use of lindane is for seed treatment, lindane has been extensively used in the past as an insecticide on a variety of crops, for home termite control, and as a wood preservative. Fate studies show that lindane is both moderately mobile (mean K_{oc} = 1368) and highly persistent (soil half life of 2.6 years). Even considering lindane's very low use rate under the current use restriction to seed treatment (maximum of 0.05 lb a.i./acre), modeling studies show that lindane concentrations in both surface and ground water may reach environmentally significant levels (> MCL). This conclusion is based solely on lindane's use as a seed treatment and does not consider past uses of lindane. However, note that lindane continues to persist in the environment from past uses.

Lindane is persistent and moderately mobile. It is resistant to photolysis and hydrolysis (except at high pH), and degrades very slowly by microbial actions. Degradates are predominantly isomers of benzene hexachloride, pentachlorocyclohexane, 1,2,4,-trichlorobenzene, and 1,2,3-trichlorobenzene. Also, lindane can possibly transform to the alpha and beta isomers of hexachlorocyclohexane by biological and phototransformation, although this issue remains to be conclusively resolved. Metabolites are not quantified since they comprise less than 10% of the total residue; they are also found in rat metabolism studies and have therefore been evaluated for their toxicologic effects.

Lindane is transported through the environment by both hydrologic and atmospheric means. Lindane has often been detected in surface and ground water, and lindane and its isomers have been detected in areas of non use (e.g., the arctic), indicating global atmospheric transport. Most of these detections resulted from a combination of lindane's past widespread use and its extreme persistence. Currently, U.S. agricultural uses of lindane are restricted to seed treatments, and application rates are quite low. Even under these restriction, however, lindane may reach water resources at levels above the MCL of 0.2 µg/L.

i. Monitoring Data

The presence of lindane in the environment, due to previous widespread agricultural use, is well documented in U.S. data bases. For example, In the U.S. EPA STORET data base, 720

detections in ground water were reported between the years 1968 and 1995, in nearly all regions of the country, with especially high numbers of detections in the South and West. For these 720 detections, the median and mean concentrations were 0.01 and 11 µg/L, respectively. For surface waters, 8775 detections were reported with median and mean concentrations of 0.005 and 0.18 µg/L. STORET Detections were reported in nearly all regions of the conterminous U.S. In the USGS NAWQA study, lindane was detected in 2.58% of surface water samples (0.67% at levels greater than 0.05 µg/L, maximum concentration reported was 0.13 µg/L). For groundwater, USGS NAWQA reported a detection frequency of 0.1 % (0.07% at levels greater than 0.01 µg/L, maximum concentration reported was 0.032 µg/L). Mean and median concentrations from monitoring data are below HED's calculated Drinking Water Levels of Comparison (See Tables 10 and 11).

ii. Ground Water

Ground water concentrations were predicted with SCIGROW. Input parameters and output and the resulting EEC are summarized in Table 7.

Table 7. SCIGROW input parameters and results for lindane.

Application Rate	1 @ 0.06 lb/acre
Aerobic Soil Half Life	980 days (mean Value)
Organic Carbon Partitioning Coefficient (K_{oc})	1367 mL/g (median Value)
EEC	0.011 µg/L

iii. Surface Water

Surface water concentrations resulting from lindane use as a seed treatment were predicted with the Tier1 assessment model, GENEEC. Table 8 presents a summary of GENEEC inputs and results.

Table 8. GENEEC input parameters and results for lindane.

Application Rate	1 x 0.0512 lb ai/acre*
Aerobic Soil Half Life	980 days (single value)
Organic Carbon Partitioning Coefficient (K_{oc})	942 mL/g (lowest value)
Peak	0.67 µg/L
4-day average	0.66 µg/L
21-day average	0.58 µg/L
56-day average	0.48 µg/L

*The highest effective application rate was for wheat at 0.0512 lb a.i. /acre

The concentrations presented in Table 9 for drinking water EECs will be used for the purposes of this risk assessment. The drinking water EECs were based on the GENEEC (surface water) and SCIGROW (groundwater) simulations described above.

Table 9. Drinking water EECs for lindane

	Acute	Chronic
Groundwater	0.011 µg/L	0.011 µg/L
Surface Water	0.67 µg/L	0.16 µg/L

* Value reported by EFED was 0.48 µg/L, current HED policy states that the average 56 day GENEEC value should be divided by 3 for chronic DWLOC calculation

F. Drinking Water Risk Estimates

Drinking water levels of comparison (DWLOCs) associated with acute and chronic exposure to lindane in drinking water have been calculated. These DWLOCs are compared with the estimated environmental concentrations (EECs) of lindane in water. The DWLOC is the concentration of a chemical in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that chemical from food, water, and residential sources. The acute and chronic DWLOC for lindane includes aggregate exposure from food and water only.

i. DWLOCs for Chronic Exposure

Chronic DWLOCs were calculated based on the chronic dietary (food) exposure estimates using lindane TRR that had been adjusted using feeding and metabolism studies as previously shown in section IV part C, along with default body weights and water consumption figures (Table 10). The EECs for surface water (GENEEC) were less than the chronic DWLOCs, indicating that chronic exposure to lindane in food and water is less than HED's level of concern. The EECs for groundwater (SCI-GROW) were less than the chronic DWLOC's, indicating that chronic exposure to lindane in food and water is less than HED's level of concern.

Table 10 Drinking Water Levels of Comparison for Chronic Dietary Exposure

Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day)	$DWLOC_{chronic}$ (ug/L)	GENEEC (ug/L)	SCI-GROW (ug/L)
US Population	0.0016	0.000054	0.001546	54	0.16	0.011
All infants < 1 yr	0.0016	0.000072	0.001528	15	0.16	0.011
Children (1-6 yrs)	0.0016	0.000173	0.001427	14	0.16	0.011
Children (7-12 yrs)	0.0016	0.000096	0.001504	15	0.16	0.011
Females (13-50 yrs)	0.0016	0.000034	0.001566	47	0.16	0.011
Males (13-19 yrs)	0.0016	0.000061	0.001539	54	0.16	0.011
Males 20+	0.0016	0.000034	0.001566	55	0.16	0.011
Seniors 55+	0.0016	0.000030	0.00157	55	0.16	0.011

The Agency's default body weights and water consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female), and 10 kg/1L (infant/children). To calculate the chronic DWLOC, the chronic dietary food exposure was subtracted from the chronic PAD as shown in the following equation:

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg/}\mapsto\text{g}]}$$

where, chronic water exposure (mg/kg/day) = [cPAD - (chronic food (mg/kg/day)]

ii. DWLOC for Acute Exposure

Acute DWLOCs were calculated based on the acute dietary exposure estimates that were determined using lindane TRR adjusted with feeding and metabolism studies as shown in section IV part C, along with default body weights and water consumption figures (Table 11). The EECs for surface water (GENEEC) were less than the acute DWLOCs for all sub-populations indicating that acute aggregate exposure to lindane in food and water is less than HED's level of concern. The GENEEC surface water value is 0.67 ppb (ug/L).

The EECs for groundwater (SCI-GROW) were less than the acute DWLOCs except for all sub-populations indicating that acute aggregate exposure to lindane in food and water is less than HED's level of concern.

The Agency's default body weights and water consumption values used to calculate DWLOCs are as follows: 70 kg/2 L (adult male), 60 kg/2 L (adult female), and 10 kg/1 L (infant/children). To calculate the DWLOC, the acute dietary food exposure was subtracted from the acute PAD using the equation:

$$DWLOC_{acute} = \frac{\text{[acute water exposure (mg/kg/day) x (body weight)]}}{\text{[consumption (L) x } 10^{-3} \text{ mg/ } \propto g]}$$

where, acute water exposure (mg/kg/day) = [aPAD - (acute food (mg/kg/day)]

Table 11. Drinking Water Levels of Comparison for Acute Dietary Exposure

Population Subgroup	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day)	$DWLOC_{acute}$ (ug/L)	GENEEC (ug/L)	SCI-GROW (ug/L)
US Population	0.02	0.0013	0.019	665	0.67	0.011
All infants < 1 yr.	0.02	0.0033	0.017	170	0.67	0.011
Children 1-6 yrs.	0.02	0.002	0.018	180	0.67	0.011
Children 7-12 yrs.	0.02	0.0011	0.019	190	0.67	0.011
Females 13-50 yrs.	0.02	0.0005	0.019	570	0.67	0.011
Males 13-19 yrs	0.02	0.0007	0.019	665	0.67	0.011
Males 20+	0.02	0.0005	0.019	665	0.67	0.011
Seniors 55+	0.02	0.0004	0.019	665	0.67	0.011

iii. Non-Dietary Exposure

Occupational lindane exposure via dermal and inhalation routes can occur during handling, mixing, loading, and applying activities. There are currently no residential pesticidal uses being supported for lindane and therefore, there is no potential for residential exposure from pesticidal uses of lindane. Based on toxicological criteria and potential for exposure, HED has conducted separate dermal and inhalation exposure assessments for a variety of occupational scenarios.

G. Occupational Exposure and Risk Estimates

There are potential exposures to mixers, loaders, applicators, or other handlers \ associated with seed treatment uses of lindane. Based on the use patterns and potential exposures described above, 5 major exposure scenarios were identified as representative of lindane uses: (1) mixing/loading/application of formulations for on-farm seed treatment, (2) mixing/ loading and applying liquid with commercial seed-treatment equipment, (3) bagging and otherwise handling treated seeds, (4) mixing/loading of treated seed for planting, (5) planting treated seeds.

Table 12 presents the exposure scenarios, application rates, and amount potentially handled that have been used for the exposure calculations. Based on submitted studies which are restricted to canola for commercial seed treatment and wheat for on farm treatments as representative of typical applications. Exposures for handling treated seed before planting and planting treated seed use parameters for wheat only, as a representative crop. Therefore, the rates/seed types presented in Table 12 are representative, rather than inclusive, and no attempt has been made to assess a range of application rates to ensure that all use rates and exposure scenarios are included.

Table 12: Exposure Variables for Uses of Lindane - Applicator/Handler Exposure

Exposure Scenario (Scenario #)	Are Chemical Specific Monitoring Data Available	Are PHED Data Available ?	Application Rates (lb ai/amt of seed)	Daily lb Seed Treated/Handled	Lb ai Handled/ day
(1)mixing/loading/application of dry formulations for on farm treatment	Yes MRID #444058-02	No	0.023 lb ai/bushel (60 lbs seed) for wheat	12000 lbs seed	4.7[a]
(2) mixing/loading and applying liquid with a commercial seed-treatment equipment	Yes Analysis from Imazalil RED (2) MRID #447315-01	No	0.04 - 1.5 lb ai/100 lb seed treated	Small: 22000	8.8- 330[b]
				Medium: 22000	8.8 - 330[b]
				Large: 165000	66 - 2500[b]
(3) handler for commercial seed-treatment equipment (i.e. bagging and stacking)	Yes Analysis from Imazalil RED (2) MRID #447315-01	No	0.04 - 1.5 lb ai/100 lb seed treated	Small: 22000	8.8 - 330[b]
				Medium: 22000	8.8 - 330[b]
				Large: 165000	66 - 2500[b]
(4) loading treated seed for planting	No	Yes	0.023 lb ai/bushel (60 lbs seed) for wheat	30000 lbs[c]	11.4[a]
(5) Planting treated seed	No	Yes	0.023 lb ai/bushel (60 lbs seed) for wheat	30000 lbs	11.4[a]

[a] Data are available from on farm treatment study (see Appendix A, D254759)

[b] Data are from a commercial seed treatment study, for example:

lb ai/day (large facility) = 0.04 lb ai/ 100 lb seed X 165000 lbs seed/ day = 66 lb ai/day

lb ai/day (medium or small facility) = 0.04 lb ai/ 100 lb seed X 22000 lbs seed/ day = 8.8 lb ai/day

[c] Daily amount treated based on HEDs estimates of acreage that would be reasonably expected to be planted in a day for commercially treated seed. The acres per day assumed 120 lbs. of wheat per acre, planting an average of 250 acres of wheat per day.

i. Commercial Seed Treatment

Several studies are available to the agency which determine the magnitude of occupational exposure as a consequence of commercial seed treatment. After review of these studies it was determined that a study (MRID 44731501) which was conducted at three seed-treatment plants in Alberta, Canada provided representative results and was most pertinent since lindane was one of the active ingredients being monitored. Worker exposure to commercial seed treatment in seed treating plants was assessed by monitoring for dermal and inhalation exposure during the loading, application, bagging, sewing, and stacking of canola seeds treated with Vitavax ® RS Flowable. The test substance is a water-based flowable seed treatment formulation containing three active ingredients, lindane (48.7 percent), thiram (6.43 percent), and carbathin/carboxin (3.34 percent). The three facilities are considered representative of large, medium and small seed-treating operations and all sites used different seed treatment equipment. A total of nine replicates were monitored in the study, (the guidelines suggests that at least 15 replicates be examined per study). Four of the replicates were categorized as loader/applicators and the remaining five workers were categorized as seed handlers. The sampling period consisted of one 8 hour work day. The maximum application rate for seed treatment of approximately 562 ml (19oz) of formulated product per 25 kg (55.31lb) seed was applied at each site. Treated seed samples were collected twice at each test site to verify the actual application rate. The study is only partially compliant with OPPTS 875 Group A test guidelines.

ii. Manual Seed Treatment

On-farm seed treatment is considered by most sources to represent a relatively small proportion of the total use of treated seed in the U.S. because of the greater time, labor, and equipment requirements as compared to those from the use of commercially treated seed. The only applicable study available to the Agency was submitted by Rhone-Poulenc, Inc. A detailed description of the study and the calculations for exposure assessment are presented in Appendix A of the Exposure Assessment Document (Jaquith, 3/01, D254759).

iii. Occupational Exposure and Risk

The daily exposures, as well as the resulting short and intermediate term MOEs are presented in Table 14. A total of 11 dermal and inhalation MOEs were calculated for the various scenarios. The analysis indicates that the MOEs are of concern (MOE<100) for commercial seed treaters who mix, load and apply a liquid formulation of lindane to canola seed at 1.5 lb/100 lb seed. Dermal MOEs range between 5.3 and 40 depending on the capacity of the seed treatment facility, and the corresponding inhalation MOEs range from 2.6 to 20. MOEs are of concern for seed handlers (those not directly handling the liquid formulation) at high capacity seed treatment facilities since the inhalation MOE is 20. On farm handling of a dry formulation

of lindane to treat seed results in a dermal MOE of 19 which is of concern. All other scenarios result in MOEs that are not of concern.

Table 13. Exposure Scenario Descriptions for the Use of Lindane.

Exposure Scenario (Scenario #)	Data Source	Standard Assumptions[a]	Comments[b]
Mixing/loading /planting dry formulation for on farm seed treatment (1)	Rhone-Poulenc Data MRID # 444058-02	Assumes enough seed treated and planted for 100 Acres per day	All data were for gloved hands; (see study, Appendix A, D254759
Mixing/loading/application of liquid formulation for commercial seed treatment (2)	Uniroyal Data MRID # 447315-01	22000 lbs of seed per day at small and medium facilities; 165000 lbs at large facilities	See study review; based on geometric mean of data and amounts of seed from study data
Seed Handler for commercial seed treatment (3)	Uniroyal Data MRID # 447315-01	22000 lbs of seed per day at small and medium facilities; 165000 lbs at large facilities	See study review; based on geometric mean of data and amounts of seed from study data
Loading treated seed for planting (4)	PHED Surrogate Table	Assumes 250 acres are planted per day at 120 lbs of seed per acre	See ORE Chapter (D254759) for data quality
Planting treated seed (5)	PHED Surrogate Table	Assumes 250 acres are planted per day at 120 lbs of seed per acre	See ORE Chapter (D254759) for data quality

a All *Standard Assumptions* are based on an 8-hour work day as estimated by HED.

[b]All handler exposure assessments in this document are based on the "Best Available" data as defined by the PHED SOP for meeting Subdivision U Guidelines (i.e., completing exposure assessments). Best available grades are assigned to data as follows: matrices with A and B grade data (i.e., Acceptable Grade Data) and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

High = grades A and B and 15 or more replicates per body part

Medium = grades A, B, and C and 15 or more replicates per body part

Low = any run that included D or E grade data or has less than 15 replicates per body part

Table 14: Daily Exposures, Short Term MOEs and Intermediate MOEs of Workers to Lindane During Seed Treatment and Planting of Treated Seed.

Exposure Scenario (Scenario #)	Application Rates (lb ai/100 lbs seed or Lb/A)	Amount Handled per Day (lbs a.i.)	Unit Exposure (mg/lb ai)		Daily Exposure (mg/kg/day)		Short-Term MOEs		Intermediate-Term MOEs	
			Dermal	Inhalation	Dermal[a]	Inhalation[b]	Dermal	Inhalation	Dermal	Inhalation
Mixing/loading/planting dry formulation for on farm seed treatment (1)	0.038	4.7	9.4[c]	0.0016	0.063	0.0001	19	1200	Intermediate-term not applicable for this scenario	
Mixing/loading/application of liquid formulation for commercial seed treatment (2)	0.04 (wheat)	8.8 (Small and Medium facilities, 22000 lbs seed/day)	0.063[d]	0.0014	0.0008	0.00018	1500	740	1500	740
		66 (Large Facility, 165000 lbs seed/day))	0.063[d]	0.0014	0.0059	0.0013	200	98	200	98
	1.5 (canola)	330(Small and Medium facilities, 22000 lbs seed/day)	0.063[d]	0.0014	0.030	0.0066	40	20	40	20
		2500 (Large Facility, 165000 lbs seed/day))	0.063[d]	0.0014	0.23	0.050	5.3	2.6	5.3	2.6

Table 14: Daily Exposures, Short Term MOEs and Intermediate MOEs of Workers to Lindane During Seed Treatment and Planting of Treated Seed.										
Exposure Scenario (Scenario #)	Application Rates (lb ai/100 lbs seed or Lb/A)	Amount Handled per Day (lbs a.i.)	Unit Exposure (mg/lb ai)		Daily Exposure (mg/kg/day)		Short-Term MOEs		Intermediate-Term MOEs	
			Dermal	Inhalation	Dermal[a]	Inhalation[b]	Dermal	Inhalation	Dermal	Inhalation
Seed Handler for commercial seed treatment (3)	0.04 (wheat)	8.8 (Small facility, 22000 lbs seed/day)	0.0022[d]	0.00018	0.00003	0.000023	43000	5700	43000	5700
		66 (Large Facility, 165000 lbs seed/day)	0.0022[d]	0.00018	0.00021	0.0002	5800	770	5800	770
	1.5 (canola)	330(Small facility, 22000 lbs seed/day)	0.0022[d]	0.00018	0.0010	0.00085	1200	150	1200	150
		2500 (Large Facility, 165000 lbs seed/day)	0.0022[d]	0.00018	0.0079	0.0064	150	20	150	20
Loading treated seed for planting (4)	0.038	11.4	0.0069[c]	0.0017	0.000046	0.00011	11000	470	Intermediate-term not applicable for this scenario	
Planting treated seed (5)	0.038	11.4	0.0021[e]	0.00022	0.000014	0.000015	35000	3600	Intermediate-term not applicable for this scenario	

[a] Daily Exposure (mg/kg/day) =mg/lb ai x lb ai/day x 0.1 (Absorption factor) ÷ 70 kb bw

[b] Daily Exposure (mg/kg/day) =mg/lb ai x lb ai/day ÷ 70 kg bw

[c] Assumes single layer of clothing and gloves

[d] Assumes coveralls over single layer of clothing and gloves

[e] Assumes closed cab, single layer of clothing and no gloves

V. Aggregate and Cumulative Exposure and Risk Characterization

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require that for establishing a pesticide tolerance "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food, and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Aggregate risk assessments are typically conducted for acute (1 day), short-term (1-7 days), intermediate-term (7 days to several months), and chronic (several months to lifetime) exposure.

A. Acute Aggregate Risk

The acute aggregate risk estimate to lindane addresses exposures from food and drinking water only since there are no residential pesticide uses remaining. The lindane acute dietary risk estimates, including all sources of residues of lindane, range from 2% to 17% of the aPAD at the 99.9th percentile of the population, with infants (<1yr) being the highest exposed population subgroup. Thus, the acute dietary (food) risk estimate associated with lindane exposure is below the Agency's level of concern.

Using conservative screening-level models, the acute estimated concentrations (EECs) of lindane in groundwater (SCI-GROW)from seed treatment uses range from 0.48 to 0.67 µg/L.

The acute surface water EECs, based on upper-bound monitoring data results, are 0.011 µg/L resulting from the use of lindane. The EECs from the use of lindane are less than the DWLOCs for all populations (the EEC of 0.011 µg/L is less than the lowest DWLOC of 170 µg/L), indicating that acute food and drinking water exposures do not exceed the Agency's level of concern. It should be noted that neither the SCI-GROW model nor the monitoring data reflect concentrations after dilution (from source to treatment to tap) or drinking water treatment. HED concludes that acute aggregate lindane exposure in food and water from the use of lindane does not exceed the Agency's level of concern. In addition, the EEC of lindane in surface water, resulting from the use of lindane, of 0.67 µg/L from the GENEEC models also indicates that acute food and drinking water exposures do not exceed the Agency's level of concern.

B. Short- and Intermediate-Term Aggregate Risk

The short- and intermediate-term aggregate risk estimate includes chronic dietary (food and water) from lindane uses, and intermediate-term non-occupational exposures (i.e., residential/ recreational uses). There are no residential/recreational seed treatment uses with a short or intermediate-term exposure scenario. Therefore, a short and intermediate-term aggregate risk estimate were not evaluated.

C. Chronic ggregate Risk

Chronic aggregate risk estimates do not exceed HED's level of concern. The aggregate chronic dietary risk estimates include exposure to lindane residues in food and water only since no chronic residential pesticide use scenarios were identified. The resulting risk estimates are 3 % of the chronic PAD (% cPAD) for the U.S. Population and 11 % of the cPAD for Children 1-6 years of age (the most highly exposed population subgroup). The remaining population subgroups were between 2% and 6 % of the cPAD when the feeding studies were adjusted using the metabolism studies. Using conservative screening-level models, the estimated average 56-day concentration of lindane in surface water resulting from seed treatment uses is 0.16 ppb. This estimated average concentration is less than HED's drinking water level of comparison for exposure to lindane in drinking water as a contribution to aggregate chronic dietary risk. Based on the available information, HED concludes with reasonable certainty that no harm to any population will result from chronic aggregate exposure to lindane.

D. Cumulative Exposure and Risk

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject

pesticide, even if the individual exposure levels to the other substances are also considered safe. For risk assessment purposes, HED has not assumed that lindane has a common mechanism of toxicity with any other chemicals at this time.

VI. Risk Characterization

The lindane risk assessment contains strengths, weaknesses, and uncertainties based on the existing toxicological and exposure data, modeling methodologies, data gaps, and gaps in scientific knowledge. This assessment uses standard assumptions regarding human body weight, work life, and other exposure parameters; and interspecies extrapolation to estimate risks. Additional assumptions were made regarding route to route extrapolation. Strengths and uncertainties of the assessment are described below.

The OPP/Cancer Assessment Review Committee (CARC) has completed the review of newly submitted carcinogenicity study in CD-1 mice along with other data. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC has classified lindane into the category **"Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"** based on an increased incidence of benign lung tumors in female mice only. The Committee, therefore, recommended that the quantification of human cancer risk is not required.

Lindane is a neurotoxicant. In acute, subchronic and developmental neurotoxicity studies, it was found to cause neurotoxic effects including tremors, convulsions, decreased motor activity, increased forelimb grip strength, hypersensitivity to touch, hunched posture and decreased motor activity habituation. There also appears to be a greater susceptibility to exposure by offspring compared to parental animals in the developmental neurotoxicity study. Lindane has also been implicated as a possible endocrine disruptor in birds, mammals and possibly fish. Further studies to ascertain the validity of such evidence is necessary to make informed risk assessment decisions.

Lindane is distributed to all organs at measurable concentrations within a few hours after oral administration. The highest concentrations are found in adipose tissue. The metabolism of lindane is initiated through one of several pathways: Dehydrogenation leading to γ-HCH, dehydrochlorination leading to formation of γ-PCCH, dechlorination leading to formation of γ-tetrachlorohexene, or hydroxylation leading to formation of hexachlorocyclohexanol. Further metabolism leads to a large number of metabolites. Lindane is converted by enzymatic reactions, mainly in the liver.

Lindane appears to affect the liver and kidney in male rats when administered through the oral, dermal or inhalation routes of exposure. Kidney lesions in males indicative of alpha 2μ globulin accumulation were observed in animals treated with ≥10 ppm, but are not considered relevant to human health risk assessment The liver effects include: incidence of periacinar hepatocytic hypertrophy which was significantly ($p \leq 0.01$) increased in male and female rats

dosed at 100 ppm (4.81 and 6.00 mg/kg/day, respectively). In addition, increased liver and spleen weights, and decreased platelets were also noted.

Lindane is not considered teratogenic when administered orally or subcutaneously. Developmental NOAELs were found to be at levels equal to or greater than maternal NOAELs, except in the developmental neurotoxicity study. The developmental neurotoxicity LOAEL was 5.6 mg/kg/day (NOAEL was 1.2 mg/kg/day) based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation compared to a maternal toxicity LOAEL of 13.7 mg/kg/day (NOAEL is 5.6 mg/kg/day) based on decreased body weight gains, decreased food consumption, and increased reactivity to handling.

The data base for reproductive toxicity is considered complete. Both parental and offspring LOAELs are 13 mg/kg; however there is a qualitative difference in the severity of effects. In the parental animals, toxicity was seen in the form of reduction in body weight gain during gestation while offspring toxicity was correlated with decreases in pup viability and pup body weight in the F_1 and F_2 generations as well as delayed maturation in the F_2 generation. Evidence for quantitative increase in susceptibility could not be ascertained due to the wide spread in the doses tested.

In a mammalian cell gene mutation assay and an in vivo sister chromatid exchange assay, no mutagenic response was detected. These studies were classified as unacceptable. The open literature suggests, however, that technical grade HCH (hexachlorohexane; 6.5% γ–HCH) may induce some mutagenic activity as evidenced in a dominant lethal mutation assay and sister chromatid exchanges. It has been noted, however, by the IPCS that lindane does not appear to have a mutagenic potential.

There are no adequate nature of the residue studies for plants from seed treatment application. New metabolism studies are required for three crops; however, a seed treatment metabolism study (which was classified as inadequate) was reviewed by the Agency and used in the determination of the TRR for use in the dietary exposure analysis. Additional residue data would be required if the HED MARC determines residues of concern include metabolites of lindane in addition to lindane *per se*. The lindane residue values were derived using a ratio of total radioactive residue divided by the amount of lindane present in the metabolism studies. This would be worst case estimate since we are assuming that all of the TRR would be residues of concern.

The dietary exposure analyses using the total radioactive residues is a Tier 3 assessment since percent crop treated was used in the analyses. The dietary exposure analyses that were based on the adjustment of the lindane residues in the feeding studies is a Tier 3 assessment. Percent market share was available for all crops included in the analyses. Since lindane is registered for seed treatments only, there is no difference in the percent crop treated values between crops grown for the fresh market and those grown for processing. A processing study

was available for canola only; the default DEEM™ processing factors were used for all other foods.

No acute or chronic residential use scenarios were identified for lindane; therefore, aggregate risk estimates address exposures from food and drinking water only. The lindane acute dietary risk estimates, including all sources of residues of lindane, range from 7% to 17% of the aPAD at the 99.9th percentile of the population, with infants (<1yr) being the highest exposed population subgroup. Thus, the acute dietary (food) risk estimate associated with lindane exposure is below the Agency's level of concern. The aggregate chronic dietary risk estimates include exposure to lindane residues in food and water. The resulting risk estimates are 3 % of the chronic PAD (% cPAD) for the U.S. Population and 11 % of the cPAD for Children 1-6 years of age (the most highly exposed population subgroup). The remaining population subgroups were <6 % of the cPAD when the total radioactive residue is adjusted using the metabolism studies. Chronic aggregate risk estimates, therefore, do not exceed HED's level of concern.

Exposure estimates for a number of occupational scenarios were derived from limited data from the submitted studies, scientific literature, and knowledge of cultural practices, in combination with models and literature studies. No residential exposure assessment was conducted by the Agency since uses have been limited to seed treatment only. The Agency considers the occupational exposure estimates to be the best available with current methodologies. Estimates of dermal and inhalation exposure to lindane in on-farm facilities are above HED's level of concern.

Volatilizalion appears to be an important route of its dissipation under the high-temperature conditions of tropical regions. The presence of lindane in the environment, due to previous widespread agricultural use, is well documented in U.S. data bases. For example, In the U.S. EPA STORET data base, 720 detections in ground water were reported between the years 1968 and 1995, in nearly all regions of the country, with especially high numbers of detections in the South and West. For these 720 detections, the median and mean concentrations were 0.01 and 11 μg/L, respectively. For surface waters, 8775 detections were reported with median and mean concentrations of 0.005 and 0.18 μg/L. STORET Detections were reported in nearly all regions of the conterminous U.S. In the USGS NAWQA study, lindane was detected in 2.58% of surface water samples (0.67% at levels greater than 0.05 μg/L, maximum concentration reported was 0.13 μg/L). For groundwater, USGS NAWQA reported a detection frequency of 0.1 % (0.07% at levels greater than 0.01 μg/L, maximum concentration reported was 0.032 μg/L).

HCH and Lindane have been found in the tissues and fat of humans living in the Arctic. It appears that lindane is transported from regions where it is used to the Arctic and has been found at detectable levels in the food supply of the indigenous populations of Alaska and the Northwest Territories. Detectable levels of lindane along with other isomers of HCH have been documented in fish, elk, caribou and other aquatic and wildlife. It persists in the air, water, and soil and continues to show patterns of long range atmospheric movement into areas where it has

been banned or never been used. The continued worldwide use of lindane may pose an environmental, as well as a human toxicologic risk to the indigenous peoples of the Arctic.

The Indigenous Peoples of the Arctic region of the U.S. (Alaska) rely heavily on subsistence diets as their food source. Thus, it is appropriate for the Agency to perform a supplementary dietary risk and exposure assessment to assess the risk to the Indigenous People from worldwide use and manufacture of lindane. HED performed a revised supplementary chronic dietary risk and exposure assessment to assess the risk to Indigenous People from worldwide use and manufacture of lindane (T. Morton, D2280076, 1/8/02). Based on this revised exposure estimate, the chronic dietary risk to male and female adult Indigenous People is below HED's level of concern. Revised estimate risks to a 10 kg child results in an estimated chronic dietary risk to an Indigenous child of 0.0002 - 0.0022 mg/kg/day (13 to 138% cPAD). It should be noted that factors such as bioaccumulation of lindane and the cumulative effects of combinations of chemicals which act through a common mode of action have not been incorporated into this assessment. As the Agency develops its cumulative risk assessment policies, if lindane is found to share a common mode of action with other chemicals, a more comprehensive evaluation of the contribution to public risk will be initiated.

This risk assessment does not at this time include an assessment of risks from exposure to lindane from uses other than seed treatment (e.g., use of lindane to treat head lice or scabies).

VII. Data Needs

Most of the Reregistration data requirements for Lindane have been fulfilled. The few remaining data requirements are described below.

A. Toxicology Data Requirements

870.3700b Prenatal developmental in rabbit

Although the prenatal developmental study in rabbits was found unacceptable, a new study is not being required at this time. The rationale for this decision is contained in the body of this document.

870.5300 Gene Mutation Mammalian Cell
870.5450 Dominant Lethal Assay
870.5915 In Vivo Sister Chromatid Exchange

No further genetic toxicity testing are required at this time. The mutagenic potential of lindane will be reevaluated in conjunction with the carcinogenicity review and a determination as to the need for further studies will occur at that time.

B. Product and Residue Chemistry Data Requirements

Product Chemistry

- All pertinent product chemistry data are satisfied for the Kanoria 99.5% T/TGAIs except additional data are required concerning UV/visible absorption (OPPTS 830.7050). Pertinent product chemistry data remain outstanding for the Inquinosa 99.5% T/TGAI concerning product identity, starting materials and production process, preliminary analysis, certified limits, oxidation/reduction, explodability, storage stability, corrosion characteristics, and UV/visible absorption (OPPTS 830.1550, 1600, 1620, 1700, 1750, 6314, 6316, 6317, 6320, and 7050). Technical products registered to Kanoria Chemicals & Industries were suspended effective 12/5/00 for failure to comply with a cost sharing agreement with Inquinosa. Therefore, all technicals registered which are repackages of the Kanoria products would be required to change suppliers. The Kanoria products are shown in data summary tables which are attached to the Revised Residue Chemistry Chapter (T. Morton, 12/11/01, D279259) for informational purposes only. The Prentiss, Drexel, and Amvac 99.5% technicals are repackaged from EPA-registered products, and all data requirements will be satisfied by data for the technical source products. Provided that the registrants submit the data required in the data summary tables for the lindane T/TGAIs in the Product and Residue Chemistry Chapters (T. Morton, 279259) and either certify that the suppliers of beginning materials and the manufacturing processes have not changed since the last comprehensive product chemistry reviews or submit complete updated product chemistry data packages, the Branch has no objections to the reregistration of lindane with respect to product chemistry data requirements.

Residue Chemistry

- The Agency will not require a new confined rotational crop study provided the registrants propose a 30-day plantback interval for leafy vegetables and a 12-month plantback interval for all other unregistered crops on all of their end-use product labels for lindane.
- New nature of the residue study is required for application of lindane as a seed treatment to a cereal grain.
- If, after submission of an acceptable cereal grain seed treatment metabolism study, the HED Metabolism Assessment Review Committee determines the residues of concern to include metabolites in addition to lindane, additional crop field trial data, magnitude of the residue in poultry and cattle, and processing studies will be required. In addition, an adequate residue analytical method and storage stability data will be required.

C. Occupational and Residential Exposure Data Requirements

Although a study addressing commercial seed treatment was submitted and used for exposure assessment, it was of poor quality and additional data reflecting this type of treatment are required.

VIII. Attachments

Revised Report of the Hazard Identification Assessment Review Committee. Suhair Shallal (6/18/01, 014595)

Report of the FQPA Safety Factor Committee. Brenda Tarplee (8/2/00; 014272)

Revised Product and Residue Chemistry Chapter. Thurston Morton (12/11/01, D279259)

Toxicology Chapter. Suhair Shallal (9/28/00, D269338)

Occupational and Residential Exposure Assessment and Revision. David Jaquith (3/2001, D254759; 6/5/2001, D275419)

Revised Dietary Exposure and Risk Estimates for Reregistration. Thurston Morton (12/13/2001, D279260)

Dietary Risk and Exposure Estimate for Lindane through Subsistence Diets for Indigenous People of Alaska. Thurston Morton (1/8/02, D280076)

Environmental Fate and Effects Chapter. Nicholas Federoff (6/22/00, D254762, D254764, D239249, D240496, D257803, D255772)